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Preparation of Multisubstituted Enamides via Rhodium-Catalyzed Carbozincation and Hydrozincation of Ynamides

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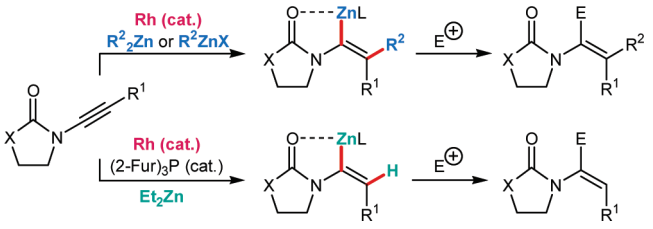

Rhodium-catalyzed carbozincation of ynamides using diorganozinc reagents or functionalized organozinc halides is described. Using a tri(2-furyl)phosphine-modified rhodium catalyst, the reaction course is altered to hydrozincation when diethylzinc is employed as the organozinc reagent. Trapping of the alkenylzinc intermediates produced in these reactions in further functionalization reactions is possible. Collectively, these processes enable access to a range of multisubstituted enamides in stereo- and regiocontrolled fashion.

Introduction

In recent years, enamides[1] have gained increasing attention as valuable synthetic intermediates for asymmetric hydrogenation[2] and a variety of other useful transformations.[1,3] In addition, the enamide moiety appears in several biologically active natural products such as TMC-95A−D,[4] crocacins A, B, and D,[5] and the salicylihalamides and related compounds.[6] Accordingly, the stereo- and regiocontrolled synthesis of enamides is an important endeavor.

Among the various strategies available to access enamides, one important class of reactions involves carbon−nitrogen bond formation on the corresponding amide, carbamate, or sulfonamide. In this context, a traditional and widely adopted approach is condensation with a carbonyl compound.[7] However, application of this method to the synthesis of more highly substituted enamides is often plagued with problems of regiocontrol and/or *E*/*Z* stereocontrol during the dehydration step,

(1) For reviews on enamides, see: (a) Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455–3460. (b) Matsubara, R.; Kobayashi, S. *Acc. Chem. Res.* **2008**, *41*, 292–301. (c) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Wiley-VCH: New York, 1999. (d) Tracey, M. R.; Hsung, R. P.; Antoline, J.; Kurtz, K. C. M.; Shen, L.; Slafer, B. W.; Zhang, Y. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Weinreb, S. M., Ed.; Georg Thieme Verlag KG: New York 1999; Chapter 21.4.

(2) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3070. (b) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103–151. (c) Brown, J. M. *Mechanism of enantioselective hydrogenation. Handbook of Homogeneous Hydrogenation*; De Vries, J. G., Elsevier, C. J., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2007. (d) Jaekel, C.; Paciello, R. *Chem. Rev.* **2006**, *106*, 2912–2942. (e) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278–1290.

(3) For recent, selected reactions of enamides, see: (a) Satyanarayana, G.; Maichle-Mössmer, C.; Maier, M. E. *Chem. Commun.* **2009**, 1571–1573. (b) Li, G.; Antilla, J. C. *Org. Lett.* **2009**, *11*, 1075–1078. (c) Friestad, G. K.; Wu, Y. *Org. Lett.* **2009**, *11*, 819–822. (d) Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun.* **2008**, 4637–4639. (e) Aciro, C.; Davies, S. G.; Garner, A. C.; Ishii, Y.; Key, M.-S.; Ling, K. B.; Prasad, R. S.; Roberts, P. M.; Rodriguez-Solla, H.; O'Leary-Steele, C.; Russell, A. J.; Sanganee, H. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron* **2008**, *64*, 9320–9344. (f) Lu, T.; Song, Z.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 541–544. (g) Berthiol, F.; Matsubara, R.; Kawai, N.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 7803–7805. (h) Song, Z.; Lu, T.; Hsung, R. P.; Al-Rashid, Z. F.; Ko, C.; Tang, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 4069–4072. (i) Gohier, F.; Bouhadjera, K.; Faye, D.; Gaulon, C.; Maisonneuve, V.; Dujardin, G.; Dhal, R. *Org. Lett.* **2007**, *9*, 211–214. (j) Ko, C.; Hsung, R. P.; Al-Rashid, Z. F.; Feltenberger, J. B.; Lu, T.; Yang, J.-H.; Wei, Y.; Zificsak, C. A. *Org. Lett.* **2007**, *9*, 4459–4462. (k) Barbazanges, M.; Meyer, C.; Cossy, J. *Org. Lett.* **2007**, *9*, 3245–3248.

(4) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990–995.

(5) (a) Kunze, B.; Jansen, R.; Höfle, G.; Reichenbach, H. *J. Antibiot.* **1994**, *47*, 881−886. (b) Jansen, R.; Washausen, P.; Kunze, B.; Reichenbach, H.; Höfle, G. *Eur. J. Org. Chem.* **1999**, 1085−1089.

(6) Yet, L. *Chem. Rev.* **2003**, *103*, 4283–4306.

(7) For an early reference, see: Zezza, C. A.; Smith, M. B. *Synth. Commun.* **1987**, *17*, 729–740.

(8) For examples of enamide synthesis relying upon palladium-catalyzed C−N bond formation, see: (a) Kozawa, Y.; Mori, M. *J. Org. Chem.* **2003**, *68*, 3064–3067. (b) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845–1848. (c) Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749–4752. (d) Klapars, A.; Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185–1188. (e) Lee, J. M.; Ahn, D.-S.; Jung, D. Y.; Lee, J.; Do, Y.; Kim, S. K.; Chang, S. *J. Am. Chem. Soc.* **2006**, *128*, 12954–12962. (f) Barluenga, J.; Moriel, P.; Aznar, F.; Valdés, C. *Org. Lett.* **2007**, *9*, 275–278.

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resulting in an unwieldy mixture of isomers. With advances in cross-coupling technology, another attractive method to prepare enamides from their parent N−H compounds is via palladium-[8] or copper-catalyzed[9] *N*-alkenylation reactions.[10] By using this approach, however, the problems of regio- and stereocontrol are now transferred to the synthesis of the alkenyl coupling partners. A further means to access enamides involving C−N bond formation is the catalytic hydroamidation of terminal alkynes.[11] Although both *E*- and *Z*-enamides may be prepared selectively,[11] this method is currently limited to the preparation of β-monosubstituted products.

A second major strategy for enamide preparation involves the use of ynamide[12] starting materials, since developments in alkynyliodonium salt chemistry[13] along with copper-[14] and iron-catalyzed[15] alkynylation methodology have meant that a variety of ynamides are now readily available. Representative intermolecular examples of this approach include hydroboration of ynamides followed by Suzuki−Miyaura coupling[16a] or homologation,[16b] hydro- or silylstannylation of ynamides followed by Stille coupling[17a,b] or lithiation−electrophilic trapping,[17c] hydrohalogenation of ynamides followed by Sonogashira coupling,[18] and various reductive coupling reactions.[19] Relevant intramolecular examples include domino Heck−Suzuki−Miyaura reactions,[20] keteniminium cyclizations,[21] ring-closing enyne metathesis,[22] and platinum-catalyzed cycloisomerizations.[23] While these reactions generally work quite well, they are often restricted to the production of only certain classes of products, or require rather specialized substrates.

Although enamides may also be prepared using a number of other methods,[24] we recently became interested in the carbometalation[25] of ynamides as a general route to multisubstituted enamides. As the majority of carbometalation reactions occur in a syn-fashion,[25] issues of selectivity during ynamide carbometalation are reduced to one of *regio*selectivity, provided isomerization does not occur. In addition, utilization of the alkenylmetal intermediates that are presumably generated during ynamide carbometalation in further functionalization reactions should allow the preparation of more highly substituted products. At least in principle therefore, ynamide carbometalation should represent one of the simplest and most flexible approaches to multisubstituted enamides.

In a seminal study, Marek and co-workers described intermolecular carbocupration and copper-catalyzed carbomagnesiation of two ynamides,[26] and this methodology has been employed by others during a study of aza-Claisen rearrangements.[27] More recently, the ynamide carbocupration variant was exploited in an interesting approach to access aldol products containing all-carbon quaternary stereocenters.[28] Despite these developments, there remains scope for improvement. For example, in the more attractive copper-catalyzed carbomagnesiation variant, the presence of base- and nucleophile-sensitive functional groups on the ynamide is restricted due to the excess Grignard reagent in solution. Furthermore, the prospects of sensitive functional

(9) For examples of enamide synthesis relying upon copper-catalyzed C−N bond formation, see: (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443–1446. (b) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333–1336. (c) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669. (d) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27–30. (e) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577–580. (f) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809–1812. (g) Shen, L.; Hsung, R. P.; Zhang, Y.; Antoline, J. E.; Zhang, X. *Org. Lett.* **2005**, *7*, 3081–3084. (h) Hu, T.; Li, C. *Org. Lett.* **2005**, *7*, 2035–2038. (i) Sun, C.; Camp, J. E.; Weinreb, S. M. *Org. Lett.* **2006**, *8*, 1779–1781. (j) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387–1390. (k) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927–4931. (l) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109–2112.

(10) For relevant reviews, see: (a) Dehli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973–986. (b) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131.

(11) (a) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413–414. (b) Goossen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042–4045. (c) Goossen, L. J.; Blanchot, M.; Brinkmann, C.; Goossen, K.; Karch, R.; Rivas-Nass, A. *J. Org. Chem.* **2006**, *71*, 9506–9509. (d) Yudha, S.; Kuninobu, Y.; Takai, K. *Org. Lett.* **2007**, *9*, 5609–5611. (e) Goossen, L. J.; Salih, K. S. M.; Blanchot, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 8492–8495. (f) Goossen, L. J.; Arndt, M.; Blanchot, M.; Rudolphi, F.; Menges, F.; Niedner-Schatteburg, G. *Adv. Synth. Catal.* **2008**, *350*, 2701–2707.

(12) For general reviews of ynamide chemistry, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575–7606. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379–1390. (c) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455–1475.

(13) For example, see: (a) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440–5452. (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489–492. (c) Witulski, B.; Gössmann, M. *Chem. Commun.* **1999**, 1879–1880. (d) Tanaka, K.; Takeishi, K.; Noguchi, K. *J. Am. Chem. Soc.* **2006**, *128*, 4586–4587.

(14) (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368–2369. (b) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011–4014. (c) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151–1154. (d) Riddell, N.; Villeneuve, K.; Tam, W. *Org. Lett.* **2005**, *7*, 3681–3684. (e) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Peterson, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170–4177. (f) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833–835. (g) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381–4385.

(15) Yao, B.; Liang, Z.; Niu, T.; Zhang, Y. *J. Org. Chem.* **2009**, *74*, 4630–4633.

(16) (a) Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473–8480. (b) Hoffmann, R. W.; Brückner, D. *New J. Chem.* **2001**, *25*, 369–373.

(17) (a) Timbart, L.; Cintrat, J. C. *Chem.—Eur. J.* **2002**, *8*, 1637–1640. (b) Buissonneaud, D.; Cintrat, J.-C. *Tetrahedron Lett.* **2006**, *47*, 3139–3143. (c) Naud, S.; Cintrat, J.-C. *Synthesis* **2003**, 1391–1397.

(18) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547–1550.

(19) (a) Saito, N.; Katayama, T.; Sato, Y. *Org. Lett.* **2008**, *10*, 3829–3832. (b) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67–70. (c) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727–729.

(20) Couty, S.; Liegault, B.; Meyer, C.; Cossy, J. *Tetrahedron* **2006**, *62*, 3882–3895.

(21) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047–1050.

(22) (a) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417–2420. (b) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803–805. (c) Mori, M.; Wakamatsu, H.; Saito, N.; Sato, Y.; Narita, R.; Sato, Y.; Fujita, R. *Tetrahedron* **2006**, *62*, 3872–3881.

(23) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509–1511.

(24) For example, see the following and references cited therein: (a) Guan, Z.-H.; Huang, K.; Yu, S.; Zhang, X. *Org. Lett.* **2009**, *11*, 481–483. (b) Savarin, C. G.; Boice, G. N.; Murry, J. A.; Corley, E.; DiMichele, L.; Hughes, D. *Org. Lett.* **2006**, *8*, 3903–3906. (c) van den Berg, M.; Haak, R. M.; Minnaard, A. J.; de Vries, A. H. M.; de Vries, J. G.; Feringa, B. L. *Adv. Synth. Catal.* **2002**, *344*, 1003–1007. (d) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084–6085. (e) Sato, M. *J. Org. Chem.* **1961**, *26*, 770–779.

(25) For general reviews on carbometalation reactions, see: (a) Marek, I.; Chinkov, N.; Banon-Tenne, D. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004; pp 395−478. (b) Marek, I.; Normant, J. F. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH, Weinheim, Germany, 1998; pp 514−522.

(26) Chechik-Lankin, H.; Livshin, S.; Marek, I. *Synlett* **2005**, 2098–2010.

(27) (a) Yasui, H.; Yorimitsu, H.; Oshima, K. *Chem. Lett.* **2007**, *36*, 32–33. (b) Yasui, H.; Yorimitsu, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2008**, *81*, 373–379.

(28) Prakash Das, J.; Chechik, H.; Marek, I. *Nature Chem.* **2009**, *1*, 128–132.

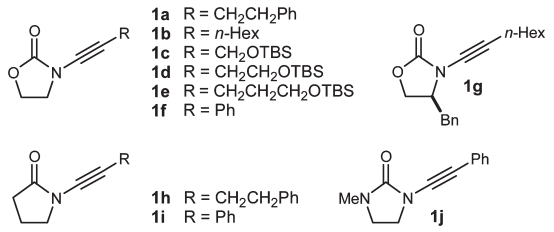


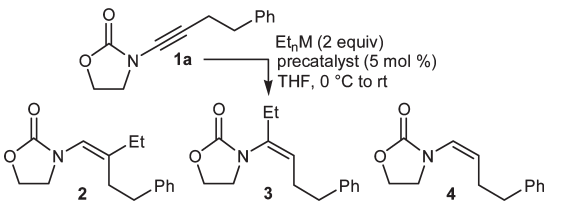
FIGURE 1. Ynamides initially examined in this study.

groups residing on the organometallic reagent itself are somewhat limited with Grignard reagents.[29] Therefore, the development of complementary ynamide carbometalation procedures using more functional group-tolerant organometallics is desirable. Recently, we described highly stereo- and regiocontrolled rhodium-catalyzed carbozincations of ynamides that enable efficient access to a range of multisubstituted enamides.[30] In this article, a more detailed account of this work is provided, including further demonstration of the utility of our catalytic system, the compatibility of the protocol with a greater range of functionalized organozinc halide reagents, the effect of exogenous ligands on the course of the reaction, and the reactivity of the alkenylzinc intermediates in further transformations with various electrophiles. Investigations into the synthetic utility of the resulting enamides and dienamides are also described.

Results and Discussion

The ynamides that were initially employed in this study are shown in Figure 1, and were prepared by copper-catalyzed *N*-alkynylation reactions of the parent N−H compound according to literature protocols.[14c,e,f] Using ynamide **1a** as a test substrate, our studies commenced with a survey of various combinations of organometallic reagents and metal salts with the goal of identifying effective conditions for carbometalation (Table 1). Conditions that were effective for carbometalation of bis-activated cyclopropenes[31] were unsuccessful with ynamide **1a** (entry 1). Using $Ni(acac)_2$ as a precatalyst, no reaction was observed with trialkylborane or trialkylaluminum reagents (entries 2 and 3), but diethylzinc was found to provide a mixture of regioisomeric addition products **2** and **3**, along with the reduction product **4**, in high conversion (entry 4).[32] Switching the precatalyst to Rh(cod)(acac), the use of Et_3B and Et_3Al gave no reaction (entries 5 and 6). However, Et_2Zn furnished enamide **2** with high regioselectivity (14:1) in 73% isolated yield in only 15 min (entry 7), with no trace of **4**. Although CuI was also an effective precatalyst, the reaction time was greatly increased to 20 h and the isolated yield of **2** was only 65% (entry 8). A control experiment performed with Et_2Zn in the absence of any precatalyst provided ca. 3−4% of **2** after 18 h, demonstrating that a slow uncatalyzed background reaction is operative (entry 9).

TABLE 1. Optimization of Carbometalation Reaction Conditions



entry	precatalyst	Et_nM	result
1	$Fe(acac)_3$	Et_3Al	complex mixture
2	$Ni(acac)_2$	Et_3B	no reaction
3		Et_3Al	no reaction
4		Et_2Zn	**2**:**3**:**4** formed in 8:1:2 ratio[a]
5	Rh(cod)(acac)	Et_3B	no reaction
6		Et_3Al	no reaction
7		Et_2Zn	**2**:**3** formed in 14:1 ratio after 15 min;[a] 73% isolated yield of **2**
8	CuI	Et_2Zn	**2**:**3** formed in >19:1 ratio after 20 h;[a] 65% isolated yield of **2**.
9	—	Et_2Zn	ca. 3−4% of **2** formed after 18 h

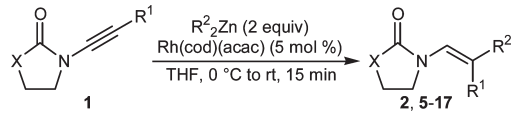
[a]Reactions proceeded to complete conversion. Ratios determined by ^1H NMR analysis of the unpurified reaction mixtures.

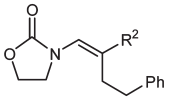
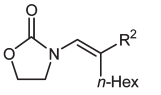
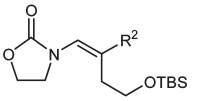
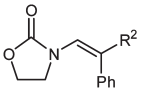
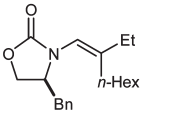
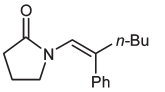
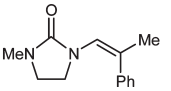
With efficient conditions in hand (Table 1, entry 7), the scope and limitation of this process was explored by using commercially available dialkylzinc reagents (Table 2). A variety of ynamides containing oxazolidin-2-one, pyrrolidin-2-one, or cyclic urea functionality smoothly underwent carbometalation with acceptable to excellent regioselectivities and generally good yields. Alkyl (entries 1−8 and 12) and aryl (entries 9−11, 13, and 14) substituents on the ynamide were tolerated, and in addition to Et_2Zn, both Me_2Zn and *n*-Bu_2Zn were effective dialkylzinc reagents for these reactions. In some cases, lower regioselectivities were observed with Me_2Zn (entries 1, 7, and 9). Ynamide **1g** containing a chiral oxazolidin-2-one was also a competent substrate, reacting smoothly with Et_2Zn to provide chiral enamide **15** (entry 12). This example bodes well for the synthesis of chiral enamides that could prove useful in a range of asymmetric reactions.[3e,f,h−j] The reaction is also successful with smaller quantities of the precatalyst and the dialkylzinc reagent, as demonstrated by carbometalation of **1f** with 2 mol % of Rh(cod)(acac) and 0.55 equiv of Et_2Zn, which provided **13** in 69% yield (entry 10). This result also shows that transfer of both alkyl groups from zinc is possible. In a few cases, small quantities of reduced products (R^2 = H) resulting from ynamide hydrometalation were detected in the unpurified reaction mixtures (entries 11 and 13), and a more detailed discussion of this phenomenon is provided later (vide infra).

Restriction of this process to the limited range of commercially available diorganozinc reagents would place a serious constraint on the generality of this methodology. Therefore, studies were undertaken to develop a method employing other readily available organometallics. Although this study was motivated by the desire to use organometallics that exhibit broad functional group tolerance, the ready availability of Grignard reagents prompted us to examine them using Rh(cod)(acac) as the precatalyst. Unfortunately, these reactions were unsuccessful, providing complex mixtures of unidentified products. Pleasingly, we discovered that the

(29) For a review of polyfunctionalized organometallics, including Grignard reagents, see: Boudier, A.; Bromm, L. O.; Lotz, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2000**, *39*, 4414–4435.
(30) Gourdet, B.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 3802–3803.
(31) Wang, Y.; Fordyce, E. A. F.; Chen, F. Y.; Lam, H. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7350–7353.
(32) For nickel-catalyzed carbozincation of arylalkynes, see: (a) Stüdemann, T.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 93–95. (b) Stüdemann, T.; Ibrahim-Ouali, M.; Knochel, P. *Tetrahedron* **1998**, *54*, 1299–1316.

TABLE 2. Rh-Catalyzed Carbozincation of Ynamides



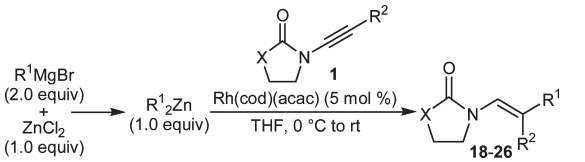
entry	ynamide	R^2	major product		rr[a]	yield (%)[b]
1	**1a**	Me		**5**	4:1	61[c]
2		Et		**2**	14:1	73
3		*n*-Bu		**6**	>19:1	85
4	**1b**	Me		**7**	9:1	63
5		Et		**8**	>19:1	78
6		*n*-Bu		**9**	10:1	81
7	**1d**	Me		**10**	5:1	49
8		Et		**11**	11:1	71
9	**1f**	Me		**12**	7:1	54
10		Et		**13**	>19:1	85 (69)[d]
11		*n*-Bu		**14**	>19:1[e]	91
12	**1g**	Et		**15**	>19:1	70
13	**1i**	*n*-Bu		**16**	>19:1[e]	75
14	**1j**	Me		**17**	>19:1	61

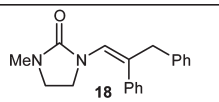
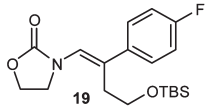
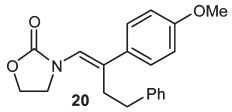
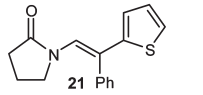
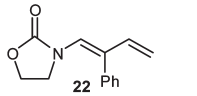
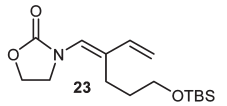
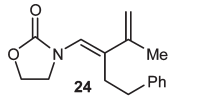
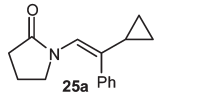
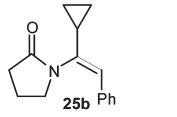
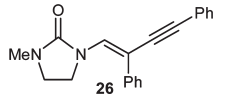
[a]rr = Regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b]Isolated yield of major regioisomer. [c]Yield of a 14:1 mixture of regioisomers. [d]Yield in parentheses refers to reaction with 2 mol % of Rh(cod)(acac) and 0.55 equiv of Et_2Zn, which took 4 h to complete. [e]Ca. 5% of the hydrometalation product (R^2 = H) was detected in the unpurified reaction mixture.

corresponding diorganozinc reagents generated in situ by transmetalation of the Grignard reagent with $ZnCl_2$ were much more effective (Table 3). For example, reaction of ynamide **1j** with dibenzylzinc (1.0 equiv) generated from BnMgCl (2.0 equiv) and $ZnCl_2$ (1.0 equiv) provided enamide **18** as the only observable regioisomer in 71% yield (entry 1). In similar fashion, carbometalation with para-substituted aromatic (entries 2 and 3) and 2-thienyl (entry 4) groups was possible, and dienamides may be accessed by carbometalation with vinyl (entries 5 and 6) and 2-propenyl (entry 7) groups. In certain cases, acceptable regioselectivities were obtained only by decreasing the reaction temperature to −78 °C (entries 4−6). The use of dicyclopropylzinc proved to be more challenging, and reaction with ynamide **1i** provided regioisomeric products **25a** and **25b** in 47% and 30% yield, respectively, even with an initial reaction temperature of −78 °C (entry 8). Transfer of an alkynyl substituent was also possible, but required a higher precatalyst loading (40%) for reasonable yields (entry 9).

While straightforward, the reliance on Grignard reagents as the source of the diorganozinc species in the reactions in Table 3 limits the presence of base- and nucleophile-sensitive functional groups in the organometallic. Although

TABLE 3. Carbozincation Using in Situ-Generated Diorganozincs



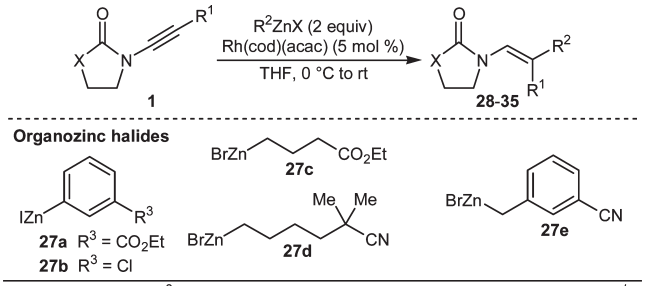
entry	ynamide	R^1	product(s)	rr[a]	yield (%)[b]
1[c]	**1j**	Bn	 **18**	>19:1	71
2	**1d**	4-F-Ph	 **19**	>19:1	84
3	**1a**	4-MeO-Ph	 **20**	>19:1	58
4[d]	**1i**	2-thienyl	 **21**	5:1	66
5[d]	**1f**	vinyl	 **22**	7:1	66
6[d]	**1e**	vinyl	 **23**	>19:1	59
7	**1a**	2-propenyl	 **24**	>19:1	47
			 **25a**		47
8[d]	**1i**	cyclopropyl	 **25b**	1.7:1	30
9[e]	**1j**	phenylethynyl	 **26**	9:1	60

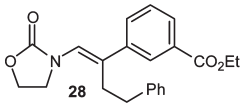
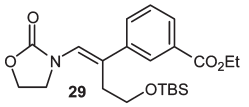
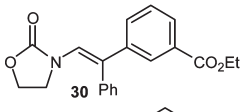
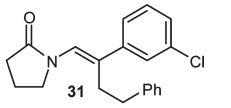
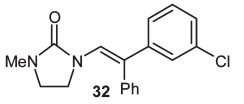
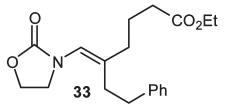
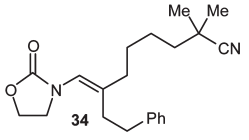
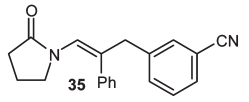
[a]rr = Regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b]Isolated yield of regioisomerically pure material. [c]Reaction conducted with BnMgCl. [d]Reaction conducted at an initial temperature of −78 °C. [e]Reaction conducted with 40 mol % of Rh(cod)(acac).

functionalized diorganozincs may be prepared by using other procedures,[33] expansion of the organometallic reagent scope to encompass organozinc halides would be attractive, since a number of these reagents (including functionalized derivatives) are now commercially available, and insertion of

(33) (a) Rozema, M. J.; Sidduri, A.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 1956–1958. (b) Vettel, S.; Vaupel, A.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 7473–7481. (c) Langer, F.; Schwink, L.; Devasagayaraj, A.; Chavant, P.-Y.; Knochel, P. *J. Org. Chem.* **1996**, *61*, 8229–8243. (d) Charette, A. B.; Beauchemin, A.; Marcoux, J.-F. *J. Am. Chem. Soc.* **1998**, *120*, 5114–5115.

TABLE 4. Carbozincation Using Organozinc Halides



entry	ynamide	R^2ZnX	major product	rr[a]	yield (%)[b]
1	**1a**	**27a**	 **28**	>19:1	75
2	**1d**	**27a**	 **29**	>19:1	66
3	**1f**	**27a**	 **30**	>19:1	58
4	**1h**	**27b**	 **31**	>19:1	77
5	**1j**	**27b**	 **32**	>19:1	82
6	**1a**	**27c**	 **33**	>19:1	54
7	**1a**	**27d**	 **34**	4:1	45[c]
8	**1i**	**27e**	 **35**	n.d.[d]	35[e]

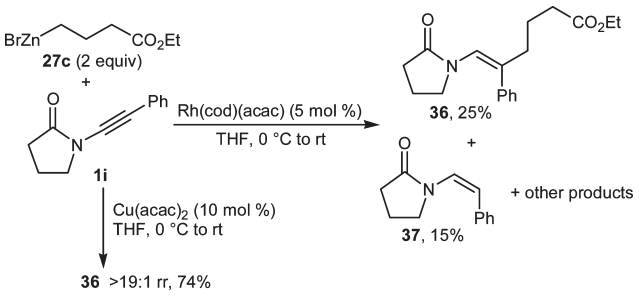
[a]rr = Regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b]Isolated yield of major regioisomer. [c]The hydrometalation product **4** was also isolated in 12% yield. [d]The ratio of isomers could not be determined due to the complexity of the unpurified reaction mixture. [e]Result obtained with $[Rh(cod)Cl]_2$ (5 mol %) and *rac*-BINAP (10 mol %) at 60 °C for 6 h.

zinc into polyfunctional iodides may be used to access a wider range of derivatives.[29,34]

Fortunately, the addition of organozinc halides was successful under our original conditions (Table 4). A variety of organozinc halide reagents were well-tolerated in the reaction; arylzinc iodides containing an ester (entries 1−3) or a chlorine (entries 4 and 5) gave the carbometalation products in generally good yields and high regioselectivities. The use of aliphatic zinc bromide reagents was also successful (entries 6 and 7), though in the case of the nitrile-substituted reagent

(34) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188.

SCHEME 1. Carbometalation of Ynamide 1i with Alkylzinc Bromide 27c



27d the regioselectivity was diminished, and the yield was lowered by a competing hydrometalation pathway (entry 7). For reasons that are unclear at this time, the benzylzinc reagent **27e** displayed sluggish reactivity, and required the use of modified conditions (5 mol % of $[Rh(cod)Cl]_2$ with 10 mol % of *rac*-BINAP at 60 °C) to deliver the product **35** in 35% yield along with other unidentified products (entry 8).

Reaction of aliphatic zinc bromide **27c** with ynamide **1i** was particularly problematic under our original conditions, and provided a complex mixture of products from which carbometalation and hydrometalation products **36** and **37** were isolated in 25% and 15% yield, respectively (Scheme 1). The remaining mass balance appeared to be composed of the regio- and/or stereoisomer of **36**, along with other unidentified products. In this case, replacement of Rh(cod)(acac) with $Cu(acac)_2$ (10 mol %) eliminated the formation of the hydrometalation product **37** and increased the regioselectivity, allowing **36** to be isolated in improved yield.[35] However, $Cu(acac)_2$ was completely ineffective in conjunction with arylzinc halide reagents, and only starting materials were recovered in these reactions.

All of the ynamides examined until this point have the carbonyl group embedded within a five-membered ring, such as an oxazolidin-2-one, pyrrolidin-2-one, or a cyclic urea. It was therefore of interest to evaluate rhodium-catalyzed carbozincations of acyclic ynamides, and representative examples of substrates studied are shown in Figure 2.

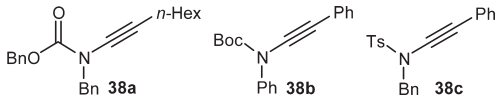
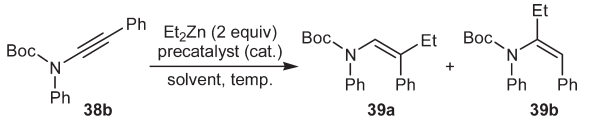


FIGURE 2. Acyclic ynamides examined in this study.

Under standard conditions with Et_2Zn as the organozinc reagent, it quickly became evident that acyclic ynamides provided unsatisfactory results. For example, ynamides containing an aliphatic substituent on the triple bond such as **38a** failed to undergo carbozincation, the only result being a small degree of substrate decomposition. Phenyl-substituted acyclic ynamides were much more reactive, and carbozincation of the Boc-protected substrate **38b** proceeded

(35) For examples of copper-catalyzed addition of organozinc halides to alkynes, see: (a) Maezaki, N.; Sawamoto, H.; Yoshigami, R.; Suzuki, T.; Tanaka, T. *Org. Lett.* **2003**, *5*, 1345–1347. (b) Maezaki, N.; Sawamoto, H.; Suzuki, T.; Yoshigami, R.; Tanaka, T. *J. Org. Chem.* **2004**, *69*, 8387–8393. (c) Sklute, G.; Bolm, C.; Marek, I. *Org. Lett.* **2007**, *9*, 1259–1261.

rapidly even at low temperatures (eq 1). Unfortunately, the selectivity of this reaction was poor, marginally favoring the unexpected regioisomer **39b**. Attempts to improve the regioselectivity through screening of ligands and solvent were unsuccessful. Although *N*-tosyl ynamide **38c** was also reactive toward rhodium-catalyzed carbozincation with Et_2Zn (products were not isolated), once again minimal regioselectivity (ca. 1:1.4) was observed.



Method A: Rh(cod)(acac) (5 mol %) THF, −78 °C, 5 min — **39a:39b** = 1:2.3, 80% (1)

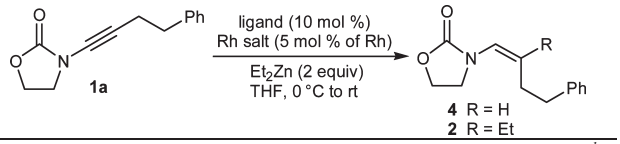
Method B: $Cu(acac)_2$ (10 mol %) Et_2O, 0 °C to rt, 16 h — **39a:39b** = >19:1, 66% (2)

In view of the improvements observed upon replacement of Rh(cod)(acac) with $Cu(acac)_2$ in the carbozincation of ynamide **1i** with alkylzinc bromide **27c** (Scheme 1), $Cu(acac)_2$ was also examined in the carbometalation of acyclic substrates **38a**−**38c** with Et_2Zn. Although **38a** and **38c** were largely inert to these conditions, improved results were observed with Boc-protected substrate **38b** with Et_2O as solvent, albeit in a much slower reaction, with enamide **39a** isolated in 66% yield and with >19:1 rr after 16 h (eq 2). Attempted carbozincations of acyclic ynamides with alkylzinc halides by using either Rh(cod)(acac) or $Cu(acac)_2$ did not provide satisfactory results, furnishing complex mixtures of products, and in the case of the copper-catalyzed procedure, low conversions were observed. Reactions of acyclic ynamides with arylzinc halides gave mostly unchanged starting materials.

We assume that the high reactivities and regioselectivities observed in the carbozincation of ynamides containing cyclic carbamate, amide, or urea groups are in part due to an efficient directing group effect[36] from the carbonyl function in coordinating to the rhodium and/or zinc centers in the carbometalation step (vide infra). Therefore, the unsatisfactory results obtained with acyclic ynamides may be a result of the greater rotational freedom of these substrates, which might be translated into diminished directing group ability of the carbonyl/sulfonyl groups. In this context, the carbocupration and copper-catalyzed carbomagnesiation reactions first described by Marek and co-workers[26−28] remain the methods of choice for carbometalation of acyclic ynamides.

During the course of these studies, hydrometalation was observed as a competing process in several cases (Table 2, entries 11 and 13; Table 4, entry 7; and Scheme 1). Presumably, this pathway occurs as a result of β-hydride elimination taking place when the organometallic reagent contains a β-hydrogen-containing alkyl group. Although the resulting β-monosubstituted *Z*-enamides are best obtained by Lindlar reduction of the corresponding ynamides,[14e,37] it was nevertheless of interest to study this hydrometalation pathway in more depth. As well as possibly providing further information about this catalyst system that could guide future developments, it was hoped the hydrometalation pathway could enable access to enamides of a substitution pattern complementary to that obtained from carbometalation (vide infra).

TABLE 5. Investigation of Ligand Effects[a]



entry	Rh salt	ligand	**4**:**2**[b]
1	$[Rh(cod)Cl]_2$	—	< 1:19
2	$Rh(cod)(MeCN)_2BF_4$	—	< 1:19
3	$RhCl(PPh_3)_3$	—	5:1
4	$[Rh(cod)Cl]_2$	Ph_3P	9:1[c]
5	$[Rh(cod)Cl]_2$	Bu_3P	< 1:19
6	$[Rh(cod)Cl]_2$	(*rac*)-BINAP	< 1:19
7	$[Rh(cod)Cl]_2$	$(p\text{-F-Ph})_3F$	> 19:1[c]
8	$[Rh(cod)Cl]_2$	$(2\text{-Thienyl})_3P$	> 19:1[c]
9	$[Rh(cod)Cl]_2$	$(2\text{-Fur})_3P$	12:1

[a]All reactions proceeded to complete conversion. Carbometalation product **2** was generally obtained in ≥19:1 regioisomeric ratio. [b]Ratios determined by ^1H NMR analysis of the unpurified reaction mixtures. [c]Hydrometalation product **4** had a stereoisomeric composition of ca. 10:1 *Z*:*E*.

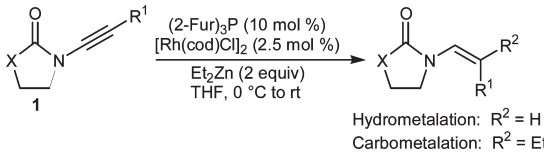
Accordingly, modification of the catalyst through variation of the rhodium source and addition of exogenous ligands was undertaken in the reaction of ynamide **1a** with Et_2Zn, with the expectation that alteration of the steric/electronic properties of the rhodium center through counterion and ligand effects could render the hydrometalation process more favorable (Table 5). Although switching the precatalyst from Rh(cod)(acac) to $[Rh(cod)Cl]_2$ or $Rh(cod)(MeCN)_2BF_4$ had minimal effect (entries 1 and 2, respectively, compare with Table 1, entry 7), Wilkinson's catalyst[38] provided a 5:1 mixture of the hydrometalation product **4** and the carbometalation product **2**, respectively (entry 3). Triphenylphosphine-modified $[Rh(cod)Cl]_2$ increased the selectivity in favor of hydrometalation further, though a small quantity of the *E*-isomer of **4** was also observed (entry 4). Use of a stronger σ-donor ligand (Bu_3P, entry 5) or a bidentate ligand (*rac*-BINAP, entry 6) switched the selectivity back in favor of carbometalation. Good π-acceptor phosphines afforded the best selectivities (≥12:1 in favor of hydrometalation, entries 7−9), though appreciable quantities of the *E*-isomer of **4** were also produced by using $(p\text{-F-Ph})_3P$ or $(2\text{-Thienyl})_3P$ (entries 7 and 8, respectively). The cleanest conversion to hydrometalation product **4** occurred with $(2\text{-Fur})_3P$ (entry 9). In all cases, reactions using phosphine-modified catalysts proceeded at a significantly decreased rate compared with those using phosphine-free precatalysts, regardless of whether hydrometalation or carbometalation was the dominant pathway (up to 6 h for complete conversion, compare with results in Table 2 which required only 15 min). Therefore, it is possible that the slow uncatalyzed background reaction (Table 1, entry 9) is responsible for small quantities of **2** observed in some of these hydrometalation reactions.

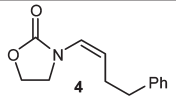
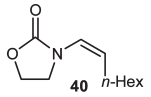
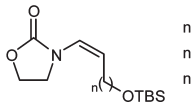
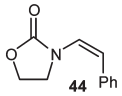
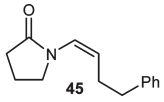
(36) For a review of substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.

(37) Other types of *Z*-enamides may be accessed efficiently through catalytic hydroamidation of terminal alkynes. See refs 11c and 11e.

(38) Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711–1732.

TABLE 6. Hydrometalation of Ynamides



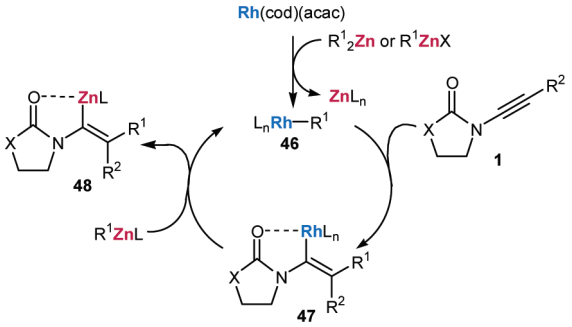
entry	ynamide	major product	selectivity[a]	yield (%)[b]
1	**1a**	 **4**	12:1	60[c]
2	**1b**	 **40**	11:1	46
3	**1c**	 n = 1: **41**	9:1	58
4	**1d**	n = 2: **42**	6:1	58[d]
5	**1e**	n = 3: **43**	6:1	42
6	**1f**	 **44**	6:3(:1)[e]	–[f]
7	**1h**	 **45**	16:1	53[d]

[a]Selectivity = ratio of hydrometalation (R^2 = H) to carbometalation (R^2 = Et) as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. [b]Unless otherwise stated, isolated yield of an inseparable mixture of hydrometalation and carbometalation product in a ratio identical with that measured from the unpurified reaction mixtures. [c]Isolated yield of a 9:1 mixture of hydrometalation product **4** and carbometalation product **2**. [d]Isolated yield of pure hydrometalation product. [e]The *E*-hydrometalation product was also detected (proportion in parentheses). [f]The complex mixture was not purified.

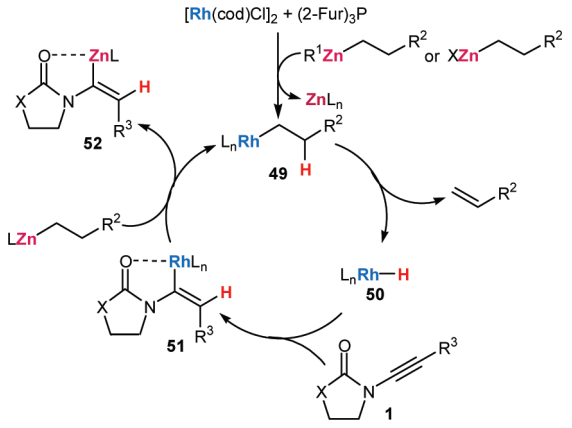
Table 6 presents the results of hydrometalation of various ynamides with Et_2Zn (2 equiv) using $[Rh(cod)Cl]_2$ (2.5 mol %) and $(2\text{-Fur})_3P$ (10 mol %). Ynamides containing oxazolidin-2-one (entries 1−6) and pyrrolidin-2-one (entry 7) functionalities successfully underwent reaction with generally reasonable-to-high selectivities in moderate yields. However, separation of the hydrometalation products from the carbometalation products by chromatography proved difficult, and the compounds were generally isolated as mixtures. Significantly lower selectivity was observed with phenyl-substituted ynamide **1f** (entry 6).

Scheme 2 illustrates a possible catalytic cycle for the carbozincation reactions. Reaction of Rh(cod)(acac) with an organozinc reagent would generate organorhodium species **46**. Syn-carbometalation of the ynamide **1** with **46** would then provide alkenylrhodium intermediate **47**.[39] Presumably, prior coordination of **46** with the carbonyl group of the ynamide is responsible for the observed regioselectivity of carbometalation.[36] Transmetalation of alkenylrhodium **47** with a further organozinc species (R^1ZnL) would then regenerate **46** and furnish alkenylzinc species **48** that is protonated upon workup. However, this mechanism may be an oversimplified representation, and involvement of an organozinc species in the carbometalation event through interactions with the ynamide carbonyl group and/or the rhodium center seems possible. Further investigations will be required to shed light on the finer details of the mechanism.

SCHEME 2. Possible Catalytic Cycle for Ynamide Carbometalation



SCHEME 3. Possible Catalytic Cycle for Ynamide Hydrometalation

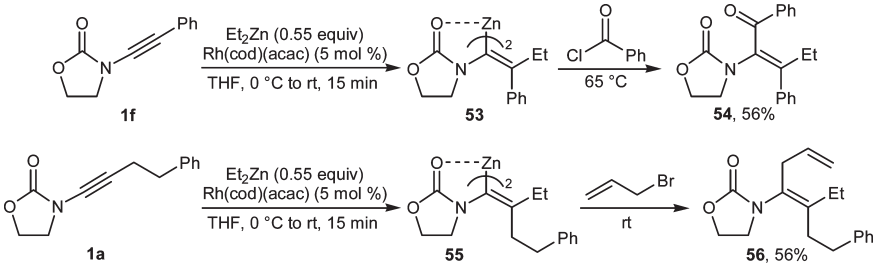


In the complementary hydrometalation procedure with $[Rh(cod)Cl]_2$ and $(2\text{-Fur})_3P$, we assume that when a β-hydrogen is present in the organorhodium species **49**, the altered electronic properties of the phosphine-ligated rhodium center leads to β-hydride elimination occurring partially at the expense of ynamide carbometalation (Scheme 3). The resulting rhodium hydride **50** then participates in a carbonyl-directed syn-hydrometalation of the ynamide **1** to provide alkenylrhodium species **51** that undergoes transmetalation with an organozinc species to give alkenylzinc species **52**, liberating **49** to reenter the catalytic cycle.

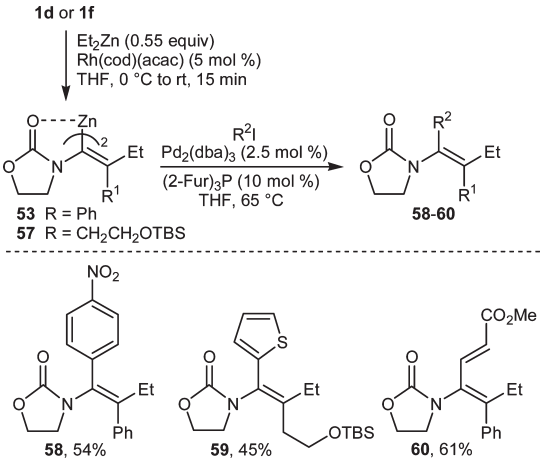
Both of these mechanisms suggested that more highly substituted enamides might be accessed through utilization of the alkenylzinc species **48** and **52** in further functionalization reactions. This strategy was first explored within the context of ynamide carbometalation. Carbozincation of ynamide **1f** with 0.55 equiv of Et_2Zn provided alkenylzinc species **53**, which could be acylated with benzoyl chloride to provide enamide **54** in 56% overall yield (Scheme 4). It was also possible to trap alkenylzinc species **55** derived from

(39) For rhodium-catalyzed conjugate addition of organozinc reagents to alkynes, see: (a) Shintani, R.; Hayashi, T. *Org. Lett.* **2005**, *7*, 2071–2073. (b) Shintani, R.; Yamagami, T.; Hayashi, T. *Org. Lett.* **2006**, *8*, 4799–4801.

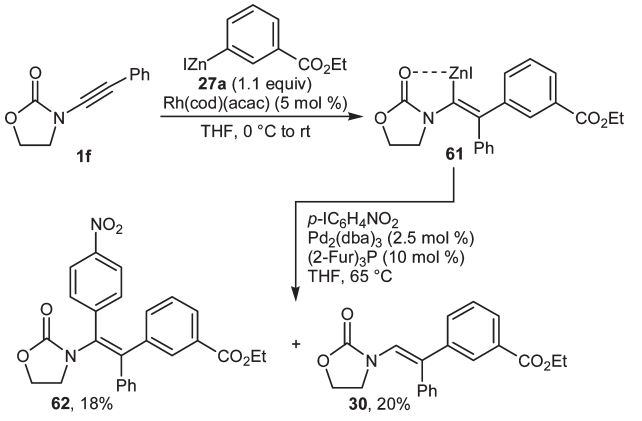
SCHEME 4. Electrophilic Trapping of Alkenylzinc Intermediates



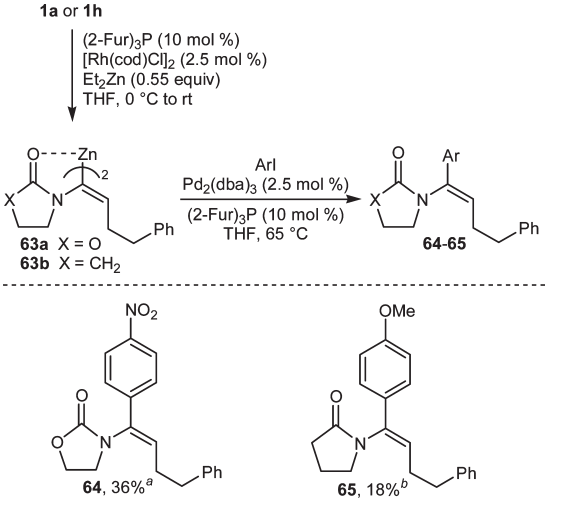
SCHEME 5. Sequential Carbozincation−Negishi Coupling



SCHEME 6. Synthesis of Triaryl-Substituted Enamide 62



SCHEME 7. Sequential Hydrozincation−Negishi Coupling



[a]Ca. 30% of the hydrometalation product **4** was detected in the unpurified reaction mixture, but was not isolated. [b]Hydrometalation product **45** was also isolated in 41% yield.

ynamide **1a** with allyl bromide to give enamide **56** in 56% yield.

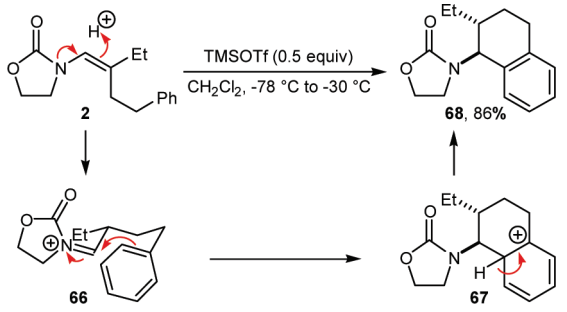
Alternatively, the alkenylzinc intermediates could be employed in Pd-catalyzed Negishi reactions[40] with aryl, heteroaryl, or alkenyl iodides by using $Pd_2(dba)_3$ (2.5 mol %) and $(2\text{-Fur})_3P$ (10 mol %) to provide enamides **58** and **59**, and dienamide **60**, respectively (Scheme 5). Furthermore, a similar sequence was possible by using an alkenylzinc species derived from carbometalation of ynamide **1f** with a functionalized arylzinc iodide, and this reaction resulted in the formation of triaryl-substituted enamide **62**, albeit in only 18% yield, along with 20% of the simple carbometalation product **30** (Scheme 6). The low yield observed in this transformation is not surprising, given the significant steric hindrance that must be overcome in the Negishi reaction.

Finally, functionalization of alkenylzinc species produced in the hydrometalation manifold was examined (Scheme 7). Sequential hydrozincation−Negishi coupling[40] was performed on ynamides **1a** and **1h** by using 0.55 equiv of Et_2Zn and two para-substituted aryl iodides to furnish the α,β-disubstituted enamides **64** and **65**, respectively. Yields were lower than those obtained in the corresponding carbozincation−Negishi process (Scheme 5), as a significant quantity of the uncoupled hydrometalation product was observed in both cases. The reasons for the unexpectedly lower efficiency of the sequential hydrozincation−Negishi process are not known at this time, though a possible explanation could lie in the altered nature of the rhodium species in the hydrometalation manifold having a deleterious effect on the palladium-catalyzed cross-coupling reaction.

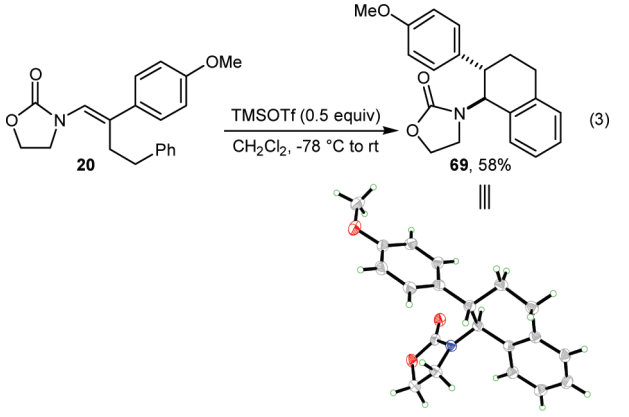
To demonstrate the synthetic utility of the enamide products, further transformations were examined. For example, treatment

(40) (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821−1823. For reviews, see: (b) Knochel, P.; Singer, R. D. *Chem. Rev.* **1993**, *93*, 2117–2188. (c) Negishi, E. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed. John Wiley & Sons: New York, 2002; Vol. 1, pp 229−247.

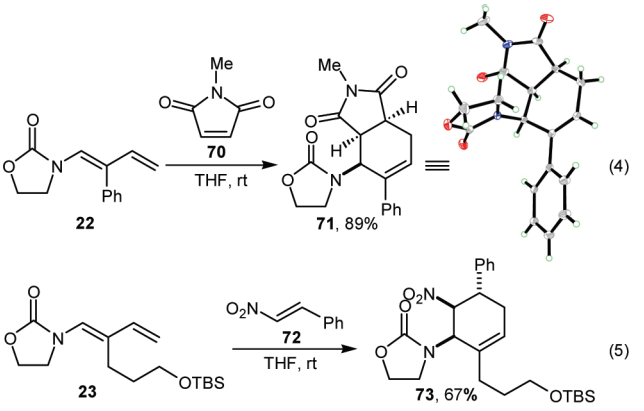
SCHEME 8. Acid-Catalyzed Cyclization of Enamide 2



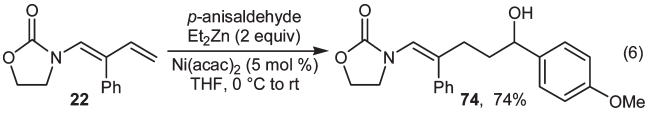
of enamide **2** with TMSOTf provided tetrahydronaphthalene **68** in 86% yield (Scheme 8). Presumably, this reaction proceeds via protonation of enamide **2** with trace TfOH present in TMSOTf,[41] Friedel–Crafts cyclization of the pendant phenyl group onto the resultant *N*-acyliminium ion **66** via a chairlike transition state with substituents in pseudoequatorial positions, followed by proton loss from **67**. In similar fashion, enamide **20** was converted into tetrahydronaphthalene **69** in 58% yield, and in this case, X-ray crystallography allowed confirmation of the relative stereochemistry of the product (eq 3).



Diels–Alder reactions of dienamides **22** and **23** that were produced by ynamide carbometalation with divinylzinc (Table 3, entries 5 and 6) are illustrated in eqs 4 and 5. Reaction of **22** with *N*-methyl maleimide (**70**) proceeded efficiently in THF at room temperature to provide bicyclic product **71** in 89% yield with high (>19:1) *endo*-selectivity (eq 4).[42] Similarly, dienamide **23** reacted with nitroalkene **72** to provide functionalized cyclohexene **73** with high selectivity (eq 5).



Tamaru and co-workers have recently developed a range of nickel-catalyzed reductive coupling reactions of dienes with carbonyl compounds that are mediated by triethylborane or diethylzinc.[43] Interestingly, the range of dienes that are tolerated in these homoallylations include siloxy-1,3-butadienes.[43d] These results prompted us to evaluate dienamides, a hitherto unexplored group of dienes in these reactions, in an analogous process. We were pleased to observe that in the presence of catalytic $Ni(acac)_2$ and Et_2Zn (2 equiv), dienamide **22** reacted smoothly with *p*-anisaldehyde in a reductive coupling reaction to provide bis-homoallylic alcohol **74** in 74% yield (eq 6).[44]



Conclusions

In summary, rhodium-catalyzed carbozincations of ynamides with diorganozinc reagents or functionalized organozinc halides have been developed, and a study of ligand effects on the course of the reaction has led to the development of a complementary hydrometalation procedure. The utility of the alkenylzinc intermediates generated in these processes has been explored in reactions with electrophiles and in palladium-catalyzed Negishi couplings, resulting in more highly substituted enamides. These methods enable the highly regio- and stereoselective synthesis of multisubstituted enamides and dienamides that would otherwise be difficult to prepare with alternative methods.

Experimental Section

General Procedure 1: Carbozincation of Ynamides with Organozinc Halide Reagents. To a solution of the appropriate ynamide (1.0 equiv) and Rh(cod)(acac) (0.05 equiv) in THF (10 mL/mmol of ynamide) at 0 °C was added the appropriate

(41) This hypothesis was supported by the following experiments: (i) The same reaction conducted in the presence of 5 mol % of TfOH provided tetrahydronaphthalene **68** in 88% yield. (ii) When enamide **2** was treated with 0.5 equiv of TMSOTf in the presence of 1 equiv of 2,6-lutidine, no reaction was observed.

(42) For examples of Diels–Alder reactions of dienamides, see: (a) Oppolzer, W.; Fröstl, W. *Helv. Chim. Acta* **1975**, *58*, 590–593. (b) Oppolzer, W.; Bieber, L.; Francotte, E. *Tetrahedron Lett.* **1979**, *20*, 4537–4540. (c) Overman, L. E.; Freerks, R. L.; Petty, C. B.; Clizbe, L. A.; Ono, R. K.; Taylor, G. F.; Jessup, P. J. *J. Am. Chem. Soc.* **1981**, *103*, 2816–2822. For examples of Diels–Alder reactions of oxazolidin-2-one-substituted dienamides, see: (d) Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J. *Tetrahedron Lett.* **1995**, *36*, 9533–9536. (e) McAlonan, H.; Murphy, J. P.; Nieuwenhuyzen, M.; Reynolds, K.; Sarma, P. K. S.; Stevenson, P. J.; Thompson, N. *J. Chem. Soc., Perkin Trans. 1* **2002**, 69–79. (f) Movassaghi, M.; Hunt, D. K.; Tjandra, M. *J. Am. Chem. Soc.* **2006**, *128*, 8126–8127. (g) Movassaghi, M.; Tjandra, M.; Qi, J. *J. Am. Chem. Soc.* **2009**, *131*, 9648–9650.

(43) (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033–4034. (b) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397–400. (c) Shibata, K.; Kimura, M.; Shimizu, M.; Tamaru, Y. *Org. Lett.* **2001**, *3*, 2181–2183. (d) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559–8568.

(44) Addition of an ethyl group to the aldehyde was found to be a competing pathway with more electrophilic substrates such as benzaldehyde.

organozinc halide (2 equiv) over 1 min, and the reaction was then stirred at room temperature until complete consumption of starting material was observed by TLC analysis. The reaction mixture was filtered through a short pad of silica gel with CH_2Cl_2 as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography afforded the desired enamide.

3-{1-[1-(2-Oxooxazolidin-3-yl)-meth-(*E*)-ylidene]-3-phenylpropyl}benzoic Acid Ethyl Ester (28). The title compound was prepared according to general procedure 1 with ynamide **1a** (43 mg, 0.20 mmol) and 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 1.5 h and purified by column chromatography (30% EtOAc/hexane) to give a yellow oil (55 mg, 75%). R_f 0.18 (30% EtOAc/hexane); IR (film) 2985, 1755 (C=O), 1714 (C=O), 1479, 1404, 1265, 1088, 1043, 908, 735 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.09 (1H, t, J = 1.6 Hz), 7.99 (1H, dt, J = 7.8, 1.4 Hz), 7.59 (1H, ddd, J = 7.8, 1.8, 1.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.30−7.26 (2H, m), 7.22−7.18 (1H, m), 7.15−7.12 (2H, m), 6.44 (1H, s), 4.42 (2H, q, J = 7.1 Hz), 4.33 (2H, app dd, J = 8.7, 7.2 Hz), 3.66−3.58 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 2.68 (2H, t, J = 7.6 Hz), 1.43 (3H, t, J = 7.1 Hz); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.5 (C), 157.0 (C), 141.2 (C), 140.5 (C), 131.2 (CH), 130.8 (C), 130.0 (C), 128.6 (CH), 128.5 (3 × CH), 128.4 (2 × CH), 127.9 (CH), 126.2 (CH), 123.4 (CH), 62.3 (CH_2), 61.1 (CH_2), 45.9 (CH_2), 34.3 (CH_2), 31.5 (CH_2), 14.3 (CH_3); HRMS (ES) exact mass calcd for $C_{22}H_{27}N_2O_4$ $[M + NH_4]^+$ 383.1965, found 383.1966.

General Procedure 2: Hydrometalation of Ynamides. To a stirred solution of the appropriate ynamide (1.0 equiv), $[Rh(cod)Cl]_2$ (0.025 equiv), and tri(2-furyl)phosphine (0.10 equiv) in THF (10 mL/mmol of ynamide) at 0 °C was added Et_2Zn (1.0 M in hexane, 2.0 equiv) over 1 min and the reaction was then stirred at room temperature until complete consumption of starting material was observed by TLC analysis (up to 6 h). The mixture was filtered through a short pad of silica gel with CH_2Cl_2 (30 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography afforded the desired enamide.

3-[(*Z*)-4-(*tert*-Butydimethylsilyloxy)but-1-enyl]oxazolidin-2-one (42). The title compound was prepared according to general procedure 2 from ynamide **1d** (133 mg, 0.50 mmol) for a reaction time of 2 h and purified by column chromatography (15% EtOAc/hexane) to give a yellow oil (79 mg, 58%). R_f 0.40 (30% EtOAc/hexane); IR (film) 2956, 2929, 2858, 1753 (C=O), 1671, 1251, 1099, 909, 736 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.35 (1H, dt, J = 9.7, 1.5 Hz), 4.81 (1H, dt, J = 9.7, 7.8 Hz), 4.38 (2H, app dd, J = 9.0, 7.0 Hz), 4.02 (2H, app dd, J = 9.0, 7.0 Hz), 3.64 (2H, t, J = 6.5 Hz), 2.39 (2H, dtd, J = 7.8, 6.5, 1.5 Hz), 0.89 (9H, s), 0.05 (6H, s); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 156.8 (C), 123.8 (CH), 110.7 (CH), 62.6 (CH_2), 62.2 (CH_2), 45.5 (CH_2), 30.1 (CH_2), 25.9 (3 × CH_3), 18.3 (C), −5.4 (2 × CH_3); HRMS (ES) exact mass calcd for $C_{13}H_{26}NO_3Si$ $[M + H]^+$ 272.1676, found 272.1677.

(±)-(3a*S*,4*S*,7a*S*)-2-Methyl-4-(2-oxooxazolidin-3-yl)-5-phenyl-3a,4,7,7a-tetrahydroisoindole-1,3-dione (71). To a solution of dienamide **22** (107 mg, 0.50 mmol) in THF (2.5 mL) was added a solution of *N*-methylmaleimide (56 mg, 0.50 mmol) in THF (2 mL + 0.5 mL rinse). The mixture was stirred at room temperature for 40 h and the solvent was removed in vacuo. Purification of the residue by column chromatography (25% EtOAc/hexane→75% EtOAc/hexane) gave the Diels−Alder product **71** as a colorless solid (145 mg, 89%). R_f 0.11 (25% EtOAc/hexane); mp 62−64 °C; IR ($CHCl_3$) 2974, 1749 (C=O), 1518, 1408, 1344, 1227, 1109, 1038, 864, 729 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36−7.26 (5H, m), 6.44 (1H, dd, J = 5.5, 3.7 Hz), 5.50 (1H, d, J = 7.3 Hz), 4.09−4.04 (2H, m), 3.50 (2H, dd, J = 9.7, 7.3 Hz), 3.29−3.20 (2H, m), 3.09 (1H, ddd, J = 8.2, 8.1, 6.3 Hz), 3.01 (3H, s), 2.87−2.70 (2H, m); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 179.3 (C), 175.9 (C), 158.0 (C), 138.1 (C), 134.4 (C), 128.9 (2 × CH), 128.1 (CH), 127.5 (CH), 125.5 (2 × CH), 61.9 (CH_2), 48.5 (CH), 43.6 (CH), 43.3 (CH_2), 37.0 (CH), 24.7 (CH_3), 22.6 (CH_2); HRMS (ES) exact mass calcd for $C_{18}H_{18}N_2O_4Na$ $[M + Na]^+$ 349.1159, found 349.1158.

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Supporting Information Available: Detailed experimental procedures, spectroscopic data for new compounds, and crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.