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Stereoselective Synthesis of Multisubstituted Enamides via Rhodium-Catalyzed Carbozincation of Ynamides

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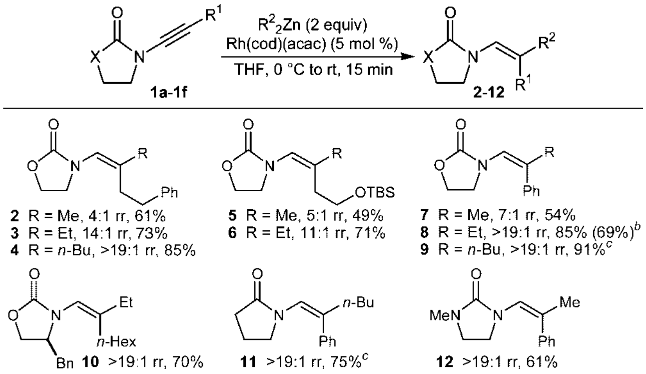
In addition to their presence in a number of natural products,[1] enamides are emerging as versatile synthetic intermediates.[2,3] Enamides may be prepared from amides, carbamates, or sulfonamides using a variety of methods, including (i) condensation with a carbonyl compound,[4] (ii) palladium- or copper-catalyzed *N*-alkenylation,[5] and (iii) catalytic hydroamidation of terminal alkynes.[6] However, control of regioselectivity and/or *E*/*Z* stereochemistry is often nontrivial in both the dehydration step of the first method and preparation of the requisite alkenyl coupling partners in the second, especially in highly substituted cases. In addition, catalytic hydroamidation[6] is limited to the preparation of β-monosubstituted enamides.

Another tactic for enamide synthesis is to conduct an appropriate transformation with an ynamide.[7] Relevant examples include vicinal addition reactions followed by cross-coupling,[8a−d] Heck cyclizations,[8e] reductive couplings,[8f−h] and keteniminium cyclizations.[8i] However, these processes are usually not general, being restricted to only certain classes of substrates.

In principle, one of the most flexible approaches for enamide synthesis is via the carbometalation[9] of ynamides.[10] Marek and coworkers have recently described intermolecular carbocupration and copper-catalyzed carbomagnesiation of two ynamides,[10a] and this methodology has been employed by others during a study of aza-Claisen rearrangements.[10b] In the more desirable catalytic variant, however, the presence of free Grignard reagents limits the presence of base- and nucleophile-sensitive functional groups on the ynamide. Therefore, there remains a need for more general ynamide carbometalation procedures to provide a greater diversity of substrates with which to study the potentially rich chemistry of enamides. Herein, we demonstrate the high efficiency of a new rhodium-catalyzed carbozincation of ynamides.

This study was initiated with evaluation of various combinations of organometallic reagents and metal salts to identify workable conditions for ynamide carbometalation.[11] These experiments revealed that using Rh(cod)(acac), cyclic ynamides **1a**−**1f**[12] containing oxazolidin-2-one, pyrrolidin-2-one, or urea functionality smoothly underwent carbometalation with Me_2Zn, Et_2Zn, and *n*-Bu_2Zn in generally good yields (Table 1). Regioselectivities were generally high, though somewhat diminished with Me_2Zn in some cases (**2**, **5**, and **7**). The reaction was tolerant of both alkyl (**2**−**6** and **10**) and aryl (**7**−**9** and **11**−**12**) groups on the ynamide, and notably, chiral enamides such as **10** that could serve as useful substrates for a range of asymmetric transformations[3b,d−f] may also be prepared using this method. Lower catalyst loadings and fewer equivalents of the dialkylzinc are also tolerated. For example, carbometalation of **1c** using 2 mol % of Rh(cod)(acac) and only 0.55 equiv of Et_2Zn proceeded smoothly to provide **8** in 69% yield, thus demonstrating that transfer of both alkyl groups from zinc is possible.

Table 1. Rh-Catalyzed Carbozincation of Assorted Ynamides[a]



2 R = Me, 4:1 rr, 61%
3 R = Et, 14:1 rr, 73%
4 R = *n*-Bu, >19:1 rr, 85%

5 R = Me, 5:1 rr, 49%
6 R = Et, 11:1 rr, 71%

7 R = Me, 7:1 rr, 54%
8 R = Et, >19:1 rr, 85% (69%)[b]
9 R = *n*-Bu, >19:1 rr, 91%[c]

10 >19:1 rr, 70%

11 >19:1 rr, 75%[c]

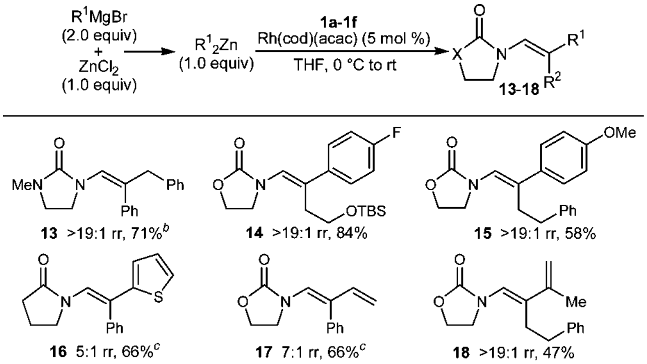
12 >19:1 rr, 61%

[a] rr = Regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Cited yields are of isolated major regioisomers. [b] Yield in parentheses refers to reaction using 2 mol % of Rh(cod)(acac) and 0.55 equiv of Et_2Zn. [c] *Ca.* 5% of a hydrometalation product (R = H) was detected in the unpurified reaction mixture.

Since only a limited number of dialkylzincs are commercially available, a procedure to engage other readily available organometallics was sought. Although Grignard reagents alone were ineffective using Rh(cod)(acac), furnishing only complex mixtures, the corresponding diorganozinc reagents generated in situ by transmetalation with $ZnCl_2$ provided excellent results (Table 2). Using this procedure, carbometalation of ynamides using benzyl (**13**), aryl (**14** and **15**), heteroaryl (**16**), and alkenyl (**17** and **18**) groups was possible. In some cases, lowering the reaction temperature to −78 °C was required to obtain acceptable regioselectivities (**16** and **17**). Utilization of *functionalized*, ester-containing alkylzinc bromide **19** was also successful (eq 1), and this result is noteworthy since a similar process would not be possible using existing ynamide carbometalation procedures.[10]

In contrast with cyclic ynamides, carbometalation of acyclic substrate **21** marginally favored the opposite regioisomer (eq 2).

Table 2. Carbozincation Using in Situ Generated Diorganozincs[a]



13 >19:1 rr, 71%[b]

14 >19:1 rr, 84%

15 >19:1 rr, 58%

16 5:1 rr, 66%[c]

17 7:1 rr, 66%[c]

18 >19:1 rr, 47%

[a] rr = Regioisomeric ratio as determined by ^{1}H NMR analysis of the unpurified reaction mixtures. Cited yields are of isolated major regioisomers. [b] Reaction conducted using BnMgCl. [c] Reaction conducted at an initial temperature of −78 °C.

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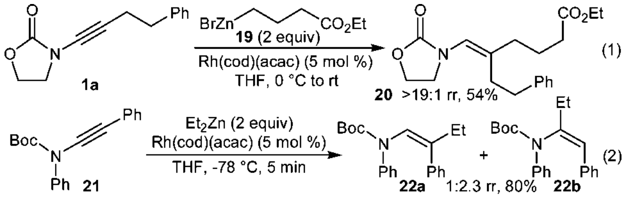
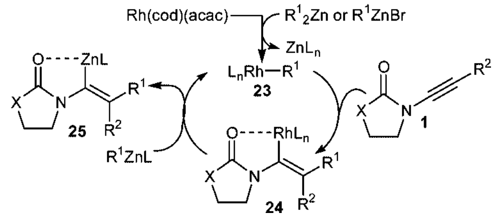
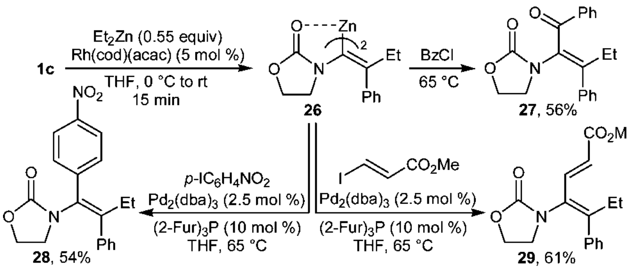


A possible catalytic cycle for these reactions is presented in Scheme 1. Presumably, reaction of Rh(cod)(acac) with an organozinc reagent would generate organorhodium species **23**. A carbonyl-directed syn-carbometalation[13] of the ynamide **1** with **23** would then provide alkenylrhodium species **24** with the regioselectivity shown, thus overriding the intrinsic polarity of ynamides. Alkenylrhodium **24** can then undergo transmetalation with an organozinc species (R^1ZnL) to regenerate **23** and give alkenylzinc **25**[14] that is protonated upon workup. This scenario suggested that more highly substituted enamides might be accessed through utilization of alkenylzinc species **25** in a further carbon−carbon bond formation.

Scheme 1. Possible Catalytic Cycle



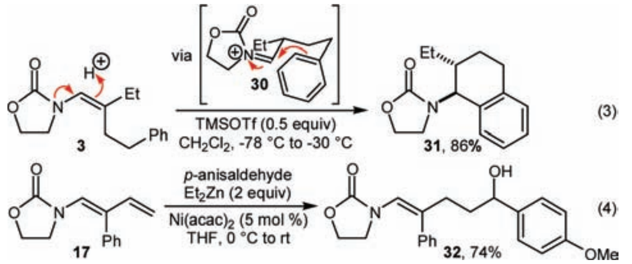
Scheme 2. Synthesis of Trisubstituted Enamides



As illustrated in Scheme 2, this feat was indeed possible. Carbozincation of ynamide **1c** with 0.55 equiv of Et_2Zn provided alkenylzinc species **26** which was acylated with benzoyl chloride to provide enamide **27** in 56% overall yield. Alternatively, Pd-catalyzed Negishi reactions[15] of **26** with an aryl or alkenyl iodide provided enamide **28** and dienamide **29**, respectively.

To demonstrate the synthetic utility of the enamide products, further transformations were examined. For example, treatment of enamide **3** with TMSOTf provided tetrahydronaphthalene **31** in 86% yield, presumably via Friedel−Crafts cyclization of the phenyl group onto the *N*-acyliminium ion **30** generated by protonation of **3** with trace TfOH present in TMSOTf (eq 3). In addition, dienamide **17** underwent smooth nickel-catalyzed reductive coupling with *p*-anisaldehyde to give **32** (eq 4).[16]

In summary, a new rhodium-catalyzed carbozincation of ynamides has been developed. This method enables the highly regio- and stereoselective synthesis of multisubstituted enamides and dienamides that would otherwise be difficult to prepare using alternative procedures and opens the door to investigation of these compounds in novel transformations. Studies along these lines are ongoing in our laboratories.



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

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