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Ruthenium-Catalyzed [2 + 2] Cycloadditions of Ynamides

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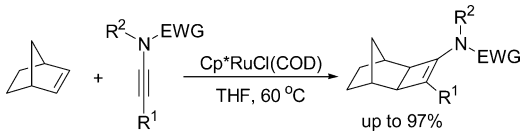
ABSTRACT



Ruthenium-catalyzed [2 + 2] cycloadditions between norbornene and ynamides were investigated. The ynamide moiety was found to be compatible with the ruthenium-catalyzed cycloaddition conditions, giving the corresponding cyclobutene cycloadducts in moderate to good yields (up to 97%).

Although ynamines and ynamides (electron-deficient ynamines) have been shown to be useful building blocks in organic synthesis,[1] their inaccessibility has limited their synthetic applications of these moieties. Recently, developments and improvements by Danheiser,[2] Hsung,[3] Cossy,[4] Sato,[5] and Witulski[6] on the synthesis of ynamines and ynamides have renewed the interest in these functional groups in the synthetic community. The interest in the applications of ynamides in organic synthesis has increased enormously in recent years due to their higher stability than ynamines. Recent studies on the synthetic versatility of ynamides include Pauson−Khand [2 + 2 + 1] cycloadditions,[7] thermal and transition metal-catalyzed [4 + 2] cycloadditions,[8] Lewis acid-catalyzed [2 + 2] cycloadditions,[9] Rh-catalyzed [2 + 2 + 2] cycloadditions,[10] ring-closing metathesis (RCM),[11] transition metal-catalyzed coupling reactions,[12] rearrangement reactions,[13] hydrometalation and hydrohalogenation reactions,[14] and cyclization reactions.[15]

We have studied various types of cycloaddition reactions of bicyclic alkenes and are especially interested in those catalyzed by transition metals.[16,17] Transition metal-catalyzed cycloadditions have demonstrated their usefulness as efficient methods in the formation of rings and complex molecules.[18] The use of transition metal catalysts provides new opportunities for highly selective cycloaddition reactions since com-

(1) For reviews of the chemistry of ynamines and ynamides, see: (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1448. (b) Collard-Motte, J.; Janousek, Z. *Top. Curr. Chem.* **1986**, *130*, 89. (c) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (d) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379.

(2) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011.

(3) (a) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (b) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. M. C.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (c) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. M. C.; Vera, E. L. *Org. Lett.* **2004**, *6*, 1151.

(4) Couty, S.; Barbazanges, M.; Meyer, C.; Cossy, J. *Synlett* **2005**, 905.

(5) Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, 727.

(6) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489.

(7) (a) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037. (b) Witulski, B.; Gößmann, M. *J. Chem. Soc., Chem. Commun.* **1999**, 1879. (c) Rainier, J. D.; Imbriglio, J. E. *J Org. Chem.* **2000**, *65*, 7272. (d) Witulski, B.; Gößmann, M. *Synlett* **2000**, 1793. (e) Shen, L. Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353.

(8) Witulski, B.; Lumtscher, J.; Bergsträßer, U. *Synlett* **2003**, 708.

(9) Hsung, R. P.; Zificsak, C. A.; Wei, L.-L.; Douglas, C. J.; Xiong, H.; Mulder, J. A. *Org. Lett.* **1999**, *1*, 1237.

(10) (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1999**, *38*, 2426. (b) Witulski, B.; Alayrac, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 3281.

(11) (a) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (b) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417.

(12) (a) Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209. (b) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511.

(13) (a) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383. (b) Frederick, M. O.; Hsung, R. P.; Lembeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663.

(14) (a) Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473. (b) Minière, S.; Cintrat, J.-C. *Synthesis* **2001**, 705. (c) Minière, S.; Cintrat, J.-C. *J. Org. Chem.* **2001**, *66*, 7385. (d) Timbart, L.; Cintrat, J.-C. *Chem. Eur. J.* **2002**, *8*, 1637. (e) 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.

(15) (a) Marion, F.; Coulomb, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509. (b) Zhang, Y.; Hsung, R. P.; Zhang, X.; Huang, J.; Slafer, B. W.; Davis, A. *Org. Lett.* **2005**, *7*, 1047.

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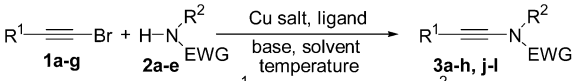
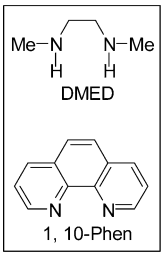
Table 1. Synthesis of Acyclic Ynamides **3a**−**h**,**j**−**l**



1a-g **2a-e** **3a-h, j-l**



3a: R^1=Ph, EWG=COOMe, R^2=Cy
3b: R^1=Ph, EWG=COOMe, R^2=CH_2CH_2Ph
3c: R^1=Ph, EWG=COOMe, R^2=CH_2Ph
3d: R^1=Ph, EWG=COO^tBu, R^2=CH_2Ph
3e: R^1=Ph, EWG=COOMe, R^2=Ph
3f: R^1=*p*-Me-C_6H_5, EWG=COOMe, R^2=Ph
3g: R^1=*o*-Me-C_6H_5, EWG=COOMe, R^2=Ph
3h: R^1=*m*-F-C_6H_5, EWG=COOMe, R^2=Ph
3j: R^1=CH_2OTBS, EWG=COOMe, R^2=Ph
3k: R^1=CH_2CH_2OTBS, EWG=COOMe, R^2=Ph
3l: R^1=$^iPr_3Si$, EWG=COOMe, R^2=Ph

entry	ynamide **3**	alkyne **1** [equiv]	amide **2** [equiv]	Cu [equiv]	base [equiv]	ligand [equiv]	solvent/temp (°C)	yield (%)[a]
1	**3a**	**1a** (2)	**2a** (1)	$CuSO_4$ (0.1)	K_2CO_3 (2.0)	Phen (0.2)	toluene/60	0
2		**1a** (2)	**2a** (1)	CuI (1.0)	KHMDS (1.0)		pyridine/25	16
3[b]		**1a** (2)	**2a** (1)	CuI (0.06)	KHMDS (1.2)	Phen (0.14)	toluene/90	43
4[b]		**1a** (2)	**2a** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.24)	toluene/90	65
5[b]	**3b**	**1a** (1)	**2a** (1.1)	CuI (0.06)	KHMDS (1.1)	DMED (0.1)	toluene/90	17
6		**1a** (1)	**2b** (1.2)	CuI (0.06)	K_2CO_3 (2.0)	DMED (0.1)	toluene/60	38
7[b]		**1a** (3)	**2b** (1)	CuI (0.08)	KHMDS (1.2)	Phen (0.12)	toluene/90	52
8	**3c**	**1a** (2)	**2c** (1)	CuI (1.0)	KHMDS (1.0)		pyridine/25	0
9		**1a** (1)	**2c** (1)	CuCN (0.06)	K_3PO_4 (2.0)	DMED (0.1)	toluene/110	0
10[b]		**1a** (2)	**2c** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.26)	toluene/90	61
11[b]	**3d**	**1a** (1)	**2d** (1.7)	CuI (0.2)	KHMDS (1.0)	Phen (0.22)	toluene/90	68
12[b]	**3e**	**1a** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.24)	toluene/90	65
13[b]	**3f**	**1b** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.27)	toluene/90	48
14[b]	**3g**	**1c** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.26)	toluene/90	39
15[b]	**3h**	**1d** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.1)	Phen (0.28)	toluene/90	54
16[b]	**3j**	**1e** (1)	**2e** (1.4)	CuI (0.4)	KHMDS (1.7)	Phen (0.46)	toluene/90	59
17[b]	**3k**	**1f** (1.4)	**2e** (1)	CuI (0.25)	KHMDS (1.0)	Phen (0.23)	toluene/90	26
18[b]	**3l**	**1g** (1.2)	**2e** (1)	CuI (0.3)	KHMDS (1.3)	Phen (0.36)	toluene/90	90

plexation of the metal to an unactivated alkene, alkyne, or diene significantly modifies the reactivity of this moiety, opening the way for enhanced reactivity and novel reactions. Recent developments in transition metal-catalyzed [2 + 2 + 1],[19] [4 + 2],[20] [5 + 2],[21] [4 + 4],[22] and [6 + 2][23] cycloaddition reactions have provided efficient methods for the construction of five- to eight-membered rings. We and others have studied various aspects of transition metal-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne for the synthesis of cyclobutene rings, including development of novel catalysts, study of the intramolecular variant of the reaction, investigation of the chemo- and regioselectivity of unsymmetrical substrates, and asymmetric

(16) For our recent contibutions on non-metal-catalyzed cycloaddition reactions of bicyclic alkenes, see: (a) Yip, C.; Handerson, S.; Jordan, R.; Tam, W. *Org. Lett.* **1999**, *1*, 791. (b) Tranmer, G. K.; Keech, P.; Tam, W. *Chem. Commun.* **2000**, 863. (c) Mayo, P.; Hecnar, T.; Tam, W. *Tetrahedron* **2001**, *57*, 5931. (d) Yip, C.; Handerson, S.; Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 276. (e) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113. (f) Tranmer, G. K.; Tam, W. *Org. Lett.* **2002**, *4*, 4101.

(17) For our recent contributions on Ru-catalyzed [2 + 2] cycloadditions, see: (a) Jordan, R. W.; Tam, W. *Org. Lett.* **2000**, *2*, 3031. (b) Jordan, R. W.; Tam, W. *Org. Lett.* **2001**, *3*, 2367. (c) Jordan, R. W.; Tam, W. *Tetrahedron Lett.* **2002**, *43*, 6051. (d) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, 2123. (e) Villeneuve, K.; Tam, W. *Angew. Chem., Int. Ed.* **2004**, 43, 610. (f) Jordan, R. W.; Khoury, P. K.; Goddard, J. D.; Tam, W. *J. Org. Chem.* **2004**, *69*, 8467. (g) Villeneuve, K.; Riddell, N.; Jordan, R. W.; Tsui, G. C.; Tam, W. *Org. Lett.* **2004**, *6*, 4543.

(18) For reviews on transition metal-catalyzed cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Hegedus, L. S. *Coord. Chem. Rev.* **1997**, *161*, 129. (c) Wender, P. A.; Love, J. A. In *Advances in Cycloaddition*; JAI Press: Greenwich, CT, 1999; Vol. 5, pp 1−45.

(19) For recent reviews on transition metal-catalyzed [2 + 2 + 1] cycloadditions, see: (a) Pericas, M. A.; Balsells, J.; Castro, J.; Marchueta, I.; Moyano, A.; Riera, A.; Vazquez, J.; Verdaguer, X. *Pure Appl. Chem.* **2002**, *74*, 167. (b) Sugihara, T.; Yamaguchi, M.; Nishizawa, M. *Chem. Eur. J.* **2001**, *7*, 1589. (c) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (d) Buchwald, S. L.; Hicks, F. A. In *Comprehensive Asymmetric Catalysis I*−*III*; Jabosen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; Vol. 2, pp 491−510. (e) Keun Chung, Y. *Coor. Chem. Rev.* **1999**, *188*, 297.

(20) (a) Wender, P. A.; Jenkins, T. E. *J. Am. Chem. Soc.* **1989**, *111*, 6432. (b) Jolly, R. S.; Luedtke, G.; Sheehan, D.; Livinghouse, T. *J. Am. Chem. Soc.* **1990**, *112*, 4965. (c) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843. (d) O'Mahoney, D. J. R.; Belanger, D. B.; Livinghouse, T. *Synlett* **1998**, 443. (e) Murakami, M.; Ubukata, M.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2248. (f) Paik, S.-J.; Son, S. U.; Chung, Y. K. *Org. Lett.* **1999**, *1*, 2045. (g) Hilt, G.; Smolko, K. I. *Angew. Chem., Int. Ed.* **2003**, *42*, 2795. (h) Witulski, B.; Lumtscher, J.; Bergsträber, U. *Synlett* **2003**, 708. (i) Hilt, G.; Lüers, S.; Harms, K. *J. Org. Chem.* **2004**, *69*, 624.

(21) (a) Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. (b) Wender, P. A.; Rieck, H.; Fuji, M. *J. Am. Chem. Soc.* **1998**, *120*, 10976. (c) Trost, B. M.; Shen, H. *Angew. Chem., Int. Ed.* **2001**, *40*, 2313. (d) Wender, P. A.; Williams, T. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 4550.

(22) (a) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. (b) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Suarez-Sobrino, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908.

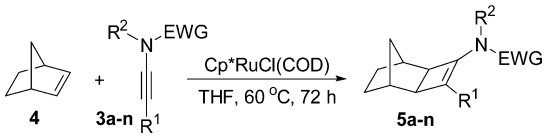
(23) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815.

induction studies using a chiral auxiliary on the alkyne component.[17,24−26] However, to the best of our knowledge, other than our recent studies of alkynyl halides in Ru-catalyzed [2 + 2] cycloadditions,[17g] all the alkynes employed thus far in transition metal-catalyzed [2 + 2] cycloadditions only contain carbon substituents such as alkyl, aryl, ester, and ketone functionalities, and the use of heteroatom-substituted acetylenic substrates in transition metal-catalyzed [2 + 2] cycloadditions is unexplored. In this paper, we report the first examples of ruthenium-catalyzed [2 + 2] cycloadditions of bicyclic alkenes with ynamides.

To begin this study, several acyclic ynamides were prepared (Table 1). Screening of various methods for the synthesis of ynamides found the methods by Danheiser[2] and Hsung[3] to be the most reliable. However, fine-tuning of the reaction conditions was required in order to optimize yields for some of the desired ynamides. For example, using Hsung's catalytic $CuSO_4$ method[3c] did not result in the formation of ynamide **3a** (entry 1), and only homocoupling of alkynyl bromide **1a** was observed. Similarly, Danheiser's stoichiometric CuI method[2] only produced ynamide **3a** in a low yield of 16% (entry 2). Reexamination of Buchwald's amidation of aryl bromide[27] suggested that the rate of deprotonation of the amide has to match the rate of the amidation reaction in order for the coupling reaction to be successful. Buchwald suggested that the formation of excess deprotonated amide deactivates the Cu catalyst by forming an unreactive cuprate complex. With this insight, we modified Hsung's catalytic CuI method[3b] by adding the base (KHMDS) slowly to the reaction mixture over 3−4 h using a syringe pump. To our delight, we were able to improve the yield of ynamide **3a** to 65% (entry 4). Similarly, for the syntheses of ynamides **3b** and **3c**, several reaction conditions were attempted, and it was found that our modified conditions gave the best results. By using these modified reaction conditions (0.2−0.3 equiv of CuI, 0.22−0.36 equiv of the 1,10-phen ligand, and adding 1.2 equiv of the base KHMDS slowly over 3−4 h in toluene at 90 °C), we obtained ynamides **3d**−**l** in moderate to good yields (entries 11−18). With these acyclic ynamides in hand, we studied their Ru-catalyzed [2 + 2] cycloadditions with norbornene **4**, and the results are shown in Table 2.

Unlike alkynes with electron-withdrawing groups attached to the acetylenic carbon (e.g., COOEt[17a] or halides[17g]), which undergo Ru-catalyzed [2 + 2] cycloadditions with bicyclic alkenes at room temperature, these ynamides with a nitrogen heteroatom attached to the acetylenic carbon were found to be less reactive and usually required an elevated temperature (60 °C) and a longer reaction time. Moderate to good yields of the Ru-catalyzed [2 + 2] cycloadditions were obtained with most of the ynamides. In all cases, single stereoisomers, the *exo* cycloadducts **5**, were formed.

Table 2. Ru-Catalyzed [2 + 2] Cycloaddition between Norbornene and Acyclic Ynamides



entry	ynamide	R^1	EWG	R^2	yield (%)[a]
1	**3a**	Ph	COOMe	Cy	55[b]
2	**3b**	Ph	COOMe	CH_2CH_2Ph	73
3	**3c**	Ph	COOMe	CH_2Ph	91
4	**3d**	Ph	COO^{t}Bu	CH_2Ph	39 (5)
5		Ph	COO^{t}Bu	CH_2Ph	75 (9)[c]
6	**3e**	Ph	COOMe	Ph	97
7	**3f**	*p*-Me-C_6H_5	COOMe	Ph	85[b]
8	**3g**	*o*-Me-C_6H_5	COOMe	Ph	49 (32)[b]
9	**3h**	*m*-F-C_6H_5	COOMe	Ph	58[d]
10	**3i**	CH_2OH	COOMe	Ph	32[d]
11	**3j**	CH_2OTBS	COOMe	Ph	25[d]
12	**3k**	CH_2CH_2OTBS	COOMe	Ph	78
13	**3l**	$^i Pr_3Si$	COOMe	Ph	0 (93)
14	**3m**	H	COOMe	Ph	0[d]
15	**3n**	COOEt	COOMe	Ph	0 (34)[d]

[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets. [b] Reaction was stirred at 60 °C for 168 h. [c] Reaction was stirred at 25 °C for 168 h. [d] Polymeric materials were also obtained on the top of the column.

Hsung previously observed an unusual *endo* cycloaddition of ynamides with bicyclic alkenes in the Co-catalyzed [2 + 2 + 1] Pauson−Khand cycloadditions.[7e] We did not observe such an unusual change in stereochemistry with our Ru-catalyzed [2 + 2] cycloadditions with ynamides.[28]

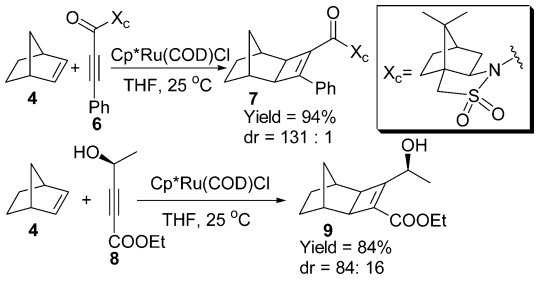
Several trends were observed in the Ru-catalyzed [2 + 2] cycloadditions of acyclic ynamides (Table 2). With ynamides **3a**−**e** (R^1 = Ph, entries 1−6), an increase in the steric bulk of the substituents (R^2 and EWG) on the nitrogen led to a decrease in the yield (compare entries 1 and 2, R^2 = 2° alkyl group vs 1° alkyl group; and compare entries 3 and 4, EWG = COOMe vs COO^{t}Bu). For ynamides **3e**−**h** (R^2 = Ph, EWG = COOMe, and R^1 = aromatic groups, entries 6−9), both the electron-withdrawing aromatic group (*m*-F-C_6H_5, entry 9) and sterically bulky aromatic group (*o*-Me-C_6H_5, entry 8) led to a decrease in the yield in the cycloaddition. Ynamides containing propargylic alcohol and propargylic silyl ether groups (entries 10 and 11) gave low yields in the cycloadditions, which may be explained by the observation of polymeric materials. Also, ynamide with a very bulky group on the alkyne (R^1 = Si^{i}Pr$_3$, entry 13) and ynamide containing an electron-withdrawing group (R^1 = COOEt, entry 15) were both inert in the Ru-catalyzed [2 + 2] cycloadditions. Terminal ynamide (R^1 = H, entry 14) gave only polymeric materials under the cycloaddition conditions.

We have recently reported the first two examples of asymmeteric induction studies of Ru-catalyzed [2 + 2] cycloadditions between an alkene and an alkyne using a chiral auxiliary attached to the alkyne component (Scheme 1).[17d,e] With the success of the Ru-catalyzed [2 + 2] cycloadditions of acyclic ynamides, we were interested to explore the reactivity and the degree of asymmeteric induc-

(24) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc.* **1993**, *115*, 5294.
(25) Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki, Y.; Watanabe, Y. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 580.
(26) (a) Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706. (b) Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C.-H. *J. Org. Chem.* **2001**, *66*, 8804.
(27) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.

(28) For determination of the *exo* and *endo* stereochemistry of [2 + 2] cycloadducts, see our previous work in ref 17.

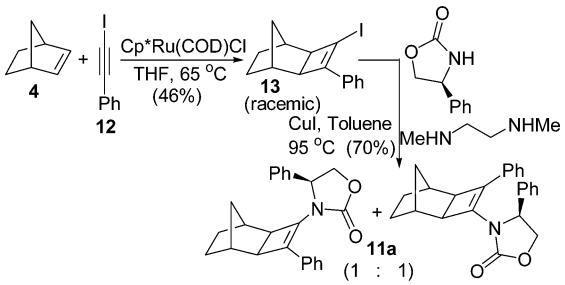
Scheme 1. Ru-Catalyzed [2 + 2] Cycloadditions between Norbornene and Alkynes Containing a Chiral Auxiliary



tion in the Ru-catalyzed [2 + 2] cycloadditions of chiral cyclic ynamides.

Several known (**10a**,**d**) and new chiral cyclic ynamides (**10b**,**c**,**e**,**f**) were synthesized,[29] and the results of the Ru-catalyzed [2 + 2] cycloadditions of these chiral cyclic ynamides are shown in Table 3. Good yields of the cycloadditions were obtained with chiral cyclic ynamides **10a**−**d** (entries 1−5); however, the diastereoselectivity was only low to moderate. The diastereomeric ratios (dr) were determined by 400 MHz ^{1}H NMR, and the peaks were compared to the 1:1 mixture of the diastereomers, which were synthesized using Buchwald's Cu-catalyzed amidation of vinyl iodide **12** (Scheme 2).[30]

Scheme 2. Synthesis of 1:1 Diastereomers of **11a**



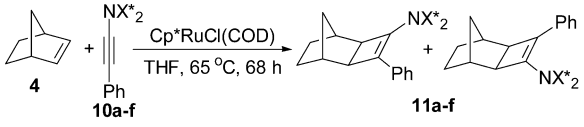
Decrease in the reaction temperature led to decrease in the yield, and no improvement of the diastereoselectivity was observed (entries 4 and 5). Ynamides **10e** and **10f** were too bulky and found to be inert in the Ru-catalyzed [2 + 2] cycloadditions (entries 6 and 7). It is worth noting that ynamide **10f** was unreactive in the Ru-catalyzed [2 + 2] cycloaddition but that amide **6** (Scheme 1), with an extra carbonyl group between the nitrogen atom and the acetylenic carbon, gave an excellent yield and excellent diastereoselectivity in the cycloaddition.

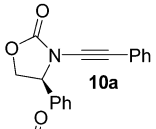
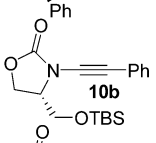
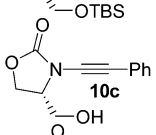
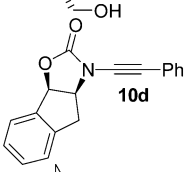
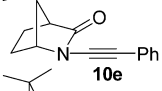
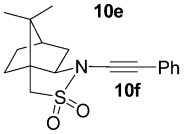
In summary, we have demonstrated the first examples of Ru-catalyzed [2 + 2] cycloadditions of ynamides. We found

(29) Known chiral ynamides **10a** and **10d** were prepared according to Hsung's method; see ref 3b. The new chiral ynamides **10e** and **10f** were synthesized using Danheiser's method; see Supporting Information for details. The new chiral ynamide **10b** was synthesized using the same method as per the synthesis of acyclic ynamides **3a**−**l**.

(30) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.

Table 3. Ru-Catalyzed [2 + 2] Cycloaddition between Norbornene and Chiral Cyclic Ynamides



entry	ynamide	yield (%)[a]	dr (%)[b]
1	 **10a**	83	72 : 28
2[c]	 **10b**	72 (7)	58 : 42
3[c]	 **10c**	81 (16)	71 : 29
4	 **10d**	82	74 : 26
5[d]		60 (39)	75 : 25
6[c]	 **10e**	0 (75)	NA
7	 **10f**	0 (94)	NA

[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets. [b] Diastereomeric ratios (drs) measured by 400 MHz ^{1}H NMR. [c] Reaction was stirred for 168 h. [d] Reaction was stirred at 25 °C for 216 h.

that the ynamide moiety is compatible with the Ru-catalyzed [2 + 2] cycloadditions and that the reactivity of ynamide functionality is generally lower than electron-deficient alkynes. Moderate to good yields of the cycloadditions were obtained with various acyclic and cyclic ynamides. However, only low to moderate levels of asymmetric induction were observed in the Ru-catalyzed [2 + 2] cycloadditions with chiral cyclic ynamides. Further investigations on the mechanism of the cycloaddition, improvement of the asymmetric induction using other chiral ynamides, and the use of the cycloadducts for the synthesis of more complex polycyclic natural products are currently in progress in our laboratory.

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

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