Heterocycles

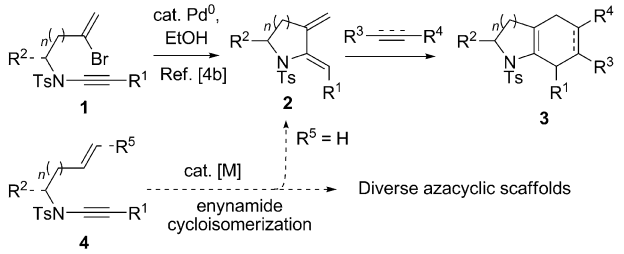
DOI: 10.1002/anie.201304186

Palladium- and Ruthenium-Catalyzed Cycloisomerization of Enynamides and Enynhydrazides: A Rapid Approach to Diverse Azacyclic Frameworks**

*P. Ross Walker, Craig D. Campbell, Abid Suleman, Greg Carr, and Edward A. Anderson**

Cycloisomerizations are amongst the most atom-economical methods to access valuable organic ring systems from simple acyclic starting materials.[1] 1,*n*-Enynes have been particularly explored as cycloisomerization substrates, thus giving rise to a broad spectrum of products depending on the choice of catalyst and substrate. In contrast, reports of 1,*n*-enynamide cycloisomerization are limited to π-acid activation of the ynamide[2] or enynamide ring-closing metathesis.[3] This is surprising given the importance of azacycles in organic and medicinal chemistry, to which enynamide cycloisomerization could provide a unique and sustainable entry.

Our group has established a program of research on the formation of azacycles from ynamides,[4,5] including palladium-catalyzed cyclization of bromoenynamides to amidodienes (**1**→**2**; Scheme 1), which are precursors to azabicycles

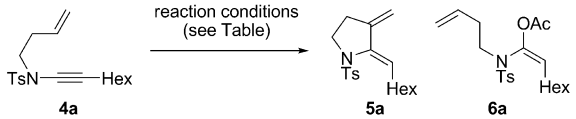


Scheme 1. Cyclizations of enynamides to 2-amidodienes. Ts = 4-toluenesulfonyl.

3 through Diels–Alder reactions.[4b] We realized that not only could we improve the atom economy of the synthesis of **2** through cycloisomerization of an enynamide **4**, but also that a far greater diversity of azacyclic products might be obtained. Here we describe the first examples of palladium-catalyzed enynamide cycloisomerization, together with contrasting ruthenium-catalyzed processes. The structural outcome of these high yielding reactions depends crucially on both the catalyst[6] and substrate substitution pattern.

With the elegant studies from Trost et al. on palladium-catalyzed 1,*n*-enyne cycloisomerization in mind,[7] we began by evaluating the cyclization of the enynamide **4a** with various palladium catalysts (Table 1). To our delight, the combination of $Pd(OAc)_2$ with either *N*,*N*′-bis(benzylidene) ethylenediamine (bbeda) or triphenylphosphine effected rapid cycloisomerization to the desired 1,3-dienamide **5a** (entries 1 and 2). In contrast, use of the bulkier ligand, P(*o*-tol)$_3$, or phosphine-free conditions, led to sluggish reactions and the formation of small amounts of the enol acetate **6a** (entries 3 and 4).[5c] Interestingly, the use of Trost's alternative reaction conditions for the generation of a palladium(II) hydride species ($[Pd_2dba_3]$/AcOH)[7c] proved effective only in the presence of bbeda (entries 5–7). [Cp*Ru(cod)Cl] has also been reported to catalyze the formation of 1,3-dienes from 1,*n*-enynes,[1c,8] and we were pleased to find that this catalyst was similarly competent in the formation of **5a**, albeit requiring an extended reaction time (entry 8).

Table 1: Optimization of enynamide cycloisomerization.[a]



Entry	Catalyst system	*t*	**5a**/**4a**/**6a**[b]
1	$Pd(OAc)_2$/bbeda	10 min	100:0:0
2	$[Pd(OAc)_2(PPh_3)_2]$	10 min	98:0:2
3	$[Pd(OAc)_2\{P(o\text{-tol})_3\}_2]$	1 h	31:62:7
4	$Pd(OAc)_2$	1 h	66:29:4
5	$[Pd_2dba_3]\cdot CHCl_3$/AcOH	1 h	50:44:6
6	$[Pd_2dba_3]\cdot CHCl_3$/AcOH/bbeda	10 min	99:0:1
7	$[Pd_2dba_3]\cdot CHCl_3$/AcOH/P(*o*-tol$_3$)	1 h	19:69:11
8	[Cp*Ru(cod)Cl][c]	1.5 h	100:0:0

[a] Reaction conditions: 5 mol% catalyst system, toluene (0.167 M), 60 °C. [b] Measured by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Performed in acetonitrile at 60 °C. Ts = 4-toluenesulfonyl; bbeda = *N*,*N*′-bis(benzylidene) ethylenediamine, cod = cyclo-1,5-octadiene, Cp* = C_5Me_5, dba = dibenzylideneacetone, *o*-tol = 2-MeC_6H_4.

With optimized reaction conditions in hand for the formation of cyclic 1,3-dienamides, we set about exploring the reaction scope (Figure 1). Alkyl-substituted 1,6-enyn-

[*] P. R. Walker,[+] Dr. C. D. Campbell,[+] Dr. E. A. Anderson
Chemistry Research Laboratory, University of Oxford
12 Mansfield Road, Oxford, OX1 3TA (UK)
E-mail: edward.anderson@chem.ox.ac.uk
Homepage: http://anderson.chem.ox.ac.uk/
A. Suleman, G. Carr
AstraZeneca, Alderley Park, Macclesfield, SK10 4TF (UK)
[+] These authors contributed equally to this work.

[**] We thank the EPSRC for an Advanced Research Fellowship (E.A.A.; EP/E055273/1) and for further funding (C.D.C.; EP/H025839/1). We also thank AstraZeneca for a CASE award (P.R.W.).
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201304186.

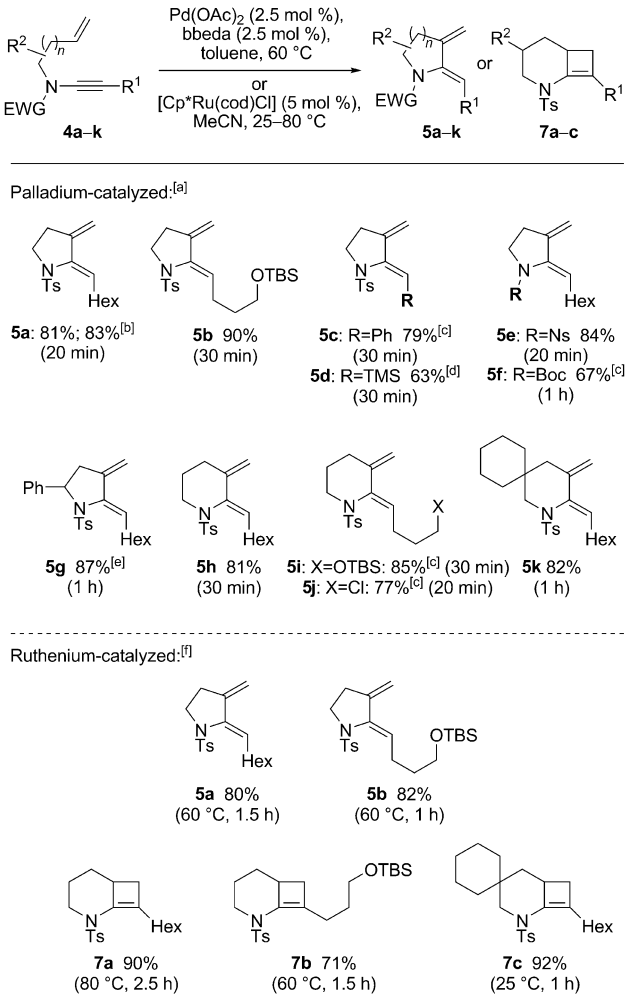


Figure 1. Cycloisomerization of monosubstituted enynamides to 1,3-dienes and bicyclic cyclobutenes. [a] Figures in parentheses indicate reaction time. Yields are those of isolated products. Products isolated as a 97:3 *Z*/*E* ratio of enamides as determined by ^{1}H NMR spectroscopic analysis of the crude reaction mixture.[9] [b] Performed on 1 g scale with 1 mol% catalyst (2.5 h). [c] Performed using 5 mol% catalyst. [d] Performed using 10 mol% catalyst. [e] Isolated as a 92:8 *Z*/*E* ratio of enamides. [f] Figures in parentheses indicate reaction temperature/time. Yields are those of isolated products. Ns = 4-$O_2NC_6H_4SO_2$, Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl.

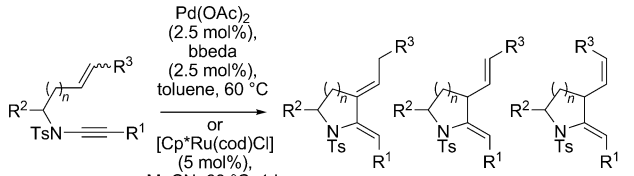
amides rapidly delivered the pyrrolidine enamides **5a** and **5b** in excellent yield with just 2.5 mol% catalyst, whilst aryl- and silyl-substituted ynamides required a slightly higher catalyst loading (5 mol%) to achieve complete conversion. Notably, the formation of **5a** could be performed in excellent yield on gram scale with just 1 mol% of the catalyst (83%), and the nature of the nitrogen electron-withdrawing group could also be varied to afford the nosyl- and Boc-protected amidodienes, **5e** and **5f**, respectively. The presence of a substituent adjacent to the sulfonamide was well-tolerated (**5g**), and high yields were also obtained for the formation of the piperidine enamides **5h–k** from 1,7-enynamides. In all cases, the reactions proved highly stereoselective, with only trace amounts of the isomeric *E* enamides being observed (*Z*/*E* = 97:3).[9]

Alkyl-substituted 1,6-enynamides were also viable substrates under ruthenium catalysis (Figure 1), which afforded the pyrrolidine enamides **5a** and **5b** as single isomers in high yield. However, a remarkable switch in reaction outcome was seen on examining 1,7-enynamides, with the 6,4-fused cyclobutenes **7a–c** being formed in excellent yields with only trace amounts of the corresponding 1,3-dienes (< 5%).[10,11] It is notable that formal [2+2] cycloadditions of ynamides usually require either electron-deficient or strained-alkene coupling partners, whereas in this intramolecular case high efficiency is observed with unstrained, electron-neutral alkenes.[12] Indeed for **7c**, this cycloisomerization occurred rapidly at room temperature, presumably due to a beneficial Thorpe–Ingold effect.

We next turned our attention to enynamides featuring 1,2-disubstituted alkenes, which have the potential to form either 1,3- or 1,4-dienes (Table 2). The cycloisomerization of enynamides with an ethyl-substituted *E* alkene (entries 1 and 2) successfully gave the *E*-1,4-dienes (*E*)-**8a** and (*E*)-**8b** as the major products, along with moderate amounts of the 1,3-diene. The analogous *Z*-alkene substrates **4n** and **4o** proved more reactive, and also favored formation of (*E*)-**8a** and (*E*)-**8b**, now to the exclusion of 1,3-diene, but with minor amounts of the *Z*-1,4-diene (entries 3 and 4). The regio- and stereoselectivity of these processes likely reflects the relative ease of β-hydride elimination from probable alkylpalladium(II) intermediates (see Scheme 3). The styrenyl ynamides **4p** and **4q**, which lack the hydrogen atoms required for 1,4-diene formation, pleasingly afforded the 1,3-dienes (*E*)-**5l** and (*Z*)-**5l**, respectively, as single stereoisomers (entries 5 and 6), further supporting the involvement of a stereospecific β-hydride elimination step. To enhance selectivity for the formation of the 1,3-diene from alkyl-substituted alkenes, we examined the cycloisomerization of allylic silyl ether **4r** (entry 7), a tactic successfully employed by Trost.[13] We found that this indeed improved selectivity for the 1,3-diene (*E*)-**5m**, which for convenience was isolated as the free alcohol after treatment with TBAF. A piperidine 1,4-dienamide could also be prepared by cycloisomerization of the 1,7-enynamide **4s** (entry 8). Finally, we were intrigued to study the potential for diastereoselective cycloisomerization. To our delight, the cyclization of the α-branched enynamides **4t** and **4u** gave the 1,4-dienes (*E*)-**8d** and (*E*)-**8e**, respectively, as single diastereomers (entries 9 and 10).[9] In the case of (*E*)-**8e**, minor amounts of 1,3-diene and a 1,5-diene arising from palladium-catalyzed alkene isomerization,[14] were also observed. This relay of stereochemistry for these substrates represents the first example of diastereoselective ynamide cycloisomerizations, and augurs well for the stereocontrolled synthesis of polysubstituted azacycles such as indolizidine and quinolizidine alkaloids.[15]

Subjecting the disubstituted enynamides to ruthenium-catalyzed cycloisomerization conditions revealed lower reactivity. Of the substrates studied, only **4k** underwent successful cycloisomerization, intriguingly giving the (*Z*,*Z*)-1,4-diene (*Z*)-**8b** as the major product (entry 11)—a result that supports the operation of different reaction pathways for the two catalyst systems (see below).

Table 2: Cycloisomerization of disubstituted alkenyl ynamides.[a]



4l–u **5l–m** (*E*)-**8a–e** (*Z*)-**8a–e**

Entry	Substrate	*n*	R^1 R^2 R^3	*T* *t*	Major product	Yield[b] **5**/(*E*)-**8**/(*Z*)-**8**[c]
1	**4l**	1	Hex H (*E*)-Et	60 °C 30 min	(*E*)-**8a**	80 % 22:78:0
2	**4m**	1	Ph H (*E*)-Et	60 °C 30 min	(*E*)-**8b**	83 % 27:70:3
3	**4n**	1	Hex H (*Z*)-Et	25 °C 1.5 h	(*E*)-**8a**	87 % 0:86:14
4	**4o**	1	Ph H (*Z*)-Et	60 °C 30 min	(*E*)-**8b**	81 % 0:91:9
5	**4p**	1	Hex H (*E*)-Ph	60 °C 4 h	(*E*)-**5l**	82 % –[d]
6	**4q**	1	Hex H (*Z*)-Ph	60 °C 20 min	(*Z*)-**5l**	84 % –[d]
7	**4r**	1	Hex H (*Z*)-CH_2OTBS	60 °C 20 min[e]	(*E*)-**5m**	53 %[f] 66:17:17
8	**4s**	2	Hex H (*Z*)-Me	60 °C 20 min[e]	**8c**	72 % 9:91
9	**4t**	1	Hex Ph (*Z*)-*n*Pr	25 °C 3 h	(*E*)-**8d**	87 % 0:100:0
10	**4u**	2	Hex Bn (*Z*)-Et	60 °C 1.5 h	(*E*)-**8e**	86 % 9:77:14[g]
11	**4m**	1	Ph H (*E*)-Et	60 °C 1 h	(*Z*)-**8b**	84 % 33:9:58[h]

[a] Reaction conditions: $Pd(OAc)_2$ (2.5 mol%), bbeda (2.5 mol%), 0.167 M in toluene. [b] Yield of isolated product. [c] Ratio of **5**/(*E*)-**8**/(*Z*)-**8** as determined by ^1H NMR spectroscopic analysis of the crude reaction mixture. [d] Formed as a single stereoisomer. [e] Performed using 5 mol% catalyst. [f] Yield of pure alcohol after treatment of the reaction mixture with TBAF. [g] 14% (by ratio) of the 1,5-diene arising from isomerization of (*E*)-**8e**. [h] Catalyzed by [Cp*Ru(cod)Cl] (5 mol%).

Having established cycloisomerizations of acyclic enynamides, we next turned to cycloalkenyl ynamides which have the potential to form a range of interesting azabicycles not readily accessible through other means (Table 3).[9] In the case of the cyclohexenyl ynamide **9a**, cyclization proceeded

Table 3: Cycloisomerization of cycloalkenyl ynamides to azabicyclic 1,4-dienes.[a]

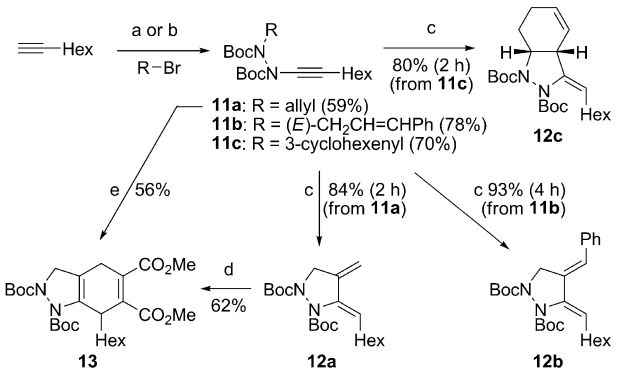
Entry	Substrate	*T* [°C]	*t* [h]	Major product	Yield [%][b]	Ratio
1	**9a**	25	2.5	**10a**	89	96:4[c]
2	**9b**	25	2.5	**10b**	91	90:10[d]
3	**9c**	60	1	**10c**	82	93:7[e]
4	**9d**	35	5	**10d**	77	91:9[c]

[a] Reaction conditions: $Pd(OAc)_2$ (2.5 mol%), bbeda (2.5 mol%), 0.167 M in toluene. [b] Yield of isolated product. [c] Ratio of *Z*/*E* enamides. [d] Ratio of 5,7-*cis*/5,7-*trans* fused rings. [e] Ratio of 1,4-diene/1,5-diene.

smoothly at room temperature to give the *cis*-fused bicycle **10a** in high yield (89%). Pleasingly, the cycloheptenyl analogue **9b** also cyclized efficiently at room temperature, thus giving the 5,7-*cis*-fused azabicycle **10b** (91%), along with a minor amount of the *trans*-fused diastereomer. Cyclization of the cyclohexenyl ynamide **9c** was similarly successful, giving the spirocyclic 1,4-diene **10c** (82%).[7c,11] Lastly, reaction of enynamide **9d** led to the bridged azabicycle **10d** (77%), a structure which bears close resemblance to the core of the alkaloid peduncularine.[16] To the best of our knowledge, this represents the first example of the use of cycloisomerization to access a bridged bicyclic system. It is of some note that this methodology is able to prepare, with high efficiency, these three distinct and challenging classes of azabicycle.

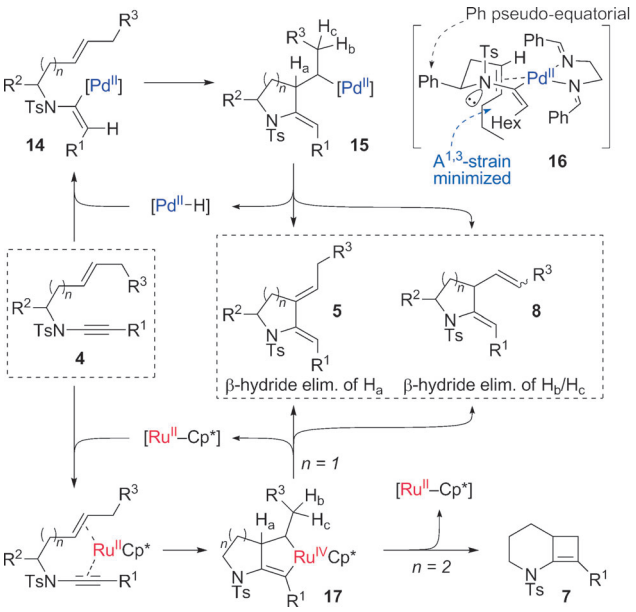
As a final extension, we were attracted to a recent approach to ynhydrazides,[17] which we found enabled a one-pot synthesis of enynhydrazides **11a–c** (Scheme 2), substrates which are unexplored in cycloisomerization, through in situ alkylation. We were delighted to find that these substrates underwent smooth cyclization at low catalyst loading (1 mol%), giving the corresponding 1,3- and 1,4-pyrazole dienes **12a–c** in excellent yields, including an attractive tetrahydroindazole framework (**12c**). These products offer many possibilities for the construction of other diazacycles. For instance, treatment of **12a** with dimethylacetylene dicarboxylate afforded the complementary tetrahydroindazole **13**. Notably, this cycloisomerization/cycloaddition sequence could also be carried out in a single step (56%), thus affording these synthetically challenging systems in just two operations from commercial materials.

The contrasting outcomes of these palladium- and ruthenium-catalyzed processes can be explained by two mecha-



Scheme 2. Synthesis and cycloisomerization of enynhydrazides. a) *n*BuLi, THF, −78 °C; BocN=NBoc; allyl bromide, 59%. b) *n*BuLi, THF, −78 °C; BocN=NBoc; R-Br, nBu_4NI (20 mol%), nBu_4NHSO_4 (20 mol%), NaOH (aq.)/toluene (1:1), 78% (**11b**, R = (*E*)-CH_2CH=CHPh), 70% (**11c**, R = 3-cyclohexenyl); c) $Pd(OAc)_2$ (1 mol%), bbeda (1 mol%), toluene 60 °C, 84%; d) $MeO_2CC{\equiv}CCO_2Me$, toluene, 80 °C, 62%. e) $Pd(OAc)_2$ (1 mol%), bbeda (1 mol%), toluene, 60 °C; then add $MeO_2CC{\equiv}CCO_2Me$, 80 °C, 56%.

nistic manifolds (Scheme 3). Under palladium catalysis, an in situ generated palladium(II) hydride species effects regioselective hydropalladation of the ynamide to afford alkenyl-



Scheme 3. Proposed cycloisomerization mechanisms.

palladium intermediate **14**. Ensuing carbopalladation gives the alkylpalladium species **15**, which (depending on the substrate) has a choice of hydrogen atoms with which to undergo β-hydride elimination. Loss of H_a delivers the 1,3-dienes **5**, whilst elimination of H_b or H_c leads to the *E*- or *Z*-1,4-dienes **8**. The highly stereoselective cyclizations of **4t** and **4u** suggest that the sulfonamide plays an important role not only as an ynamide/enamide stabilizing group, but also as a fluxional stereogenic center. The stereoselectivity (for **4t**) can be explained by conformation **16**, which minimizes 1,3-allylic strain between the ynamide side chain and tosyl group, places the phenyl substituent in a pseudo-equatorial position, and orients the alkenyl side chain pseudo-axial to avoid unfavorable steric interactions with the bbeda ligand (a similar model can be used to rationalize the cyclization of **4u**). Under ruthenium catalysis, initial complexation of the catalyst to both the alkene and ynamide enables ruthenacycle formation (**17**). With a six-membered tether, direct reductive elimination then leads to the 6,4-fused cyclobutene product **7**. However for 5,5-fused ruthenacycles, developing ring strain presumably prohibits reductive elimination, and instead β-hydride elimination affords the diene products, albeit in differing ratios to those obtained under palladium catalysis.

In conclusion, we have demonstrated that alkenyl ynamides and ynhydrazides, which are readily prepared from simple precursors, undergo high yielding cycloisomerizations under palladium and ruthenium catalysis. These operationally simple processes occur with high stereo- and regioselectivity, affording a wide diversity of attractive azacyclic scaffolds. The reactions are tolerant of a range of substituents on both the ynamide and alkene, underlining their potential utility as an atom-economical source of azacycles.

Received: May 15, 2013
Published online: July 16, 2013

Keywords: cyclization · heterocycles · homogeneous catalysis · palladium · ynamide

[1] For recent reviews, see: a) A. Marinetti, H. Jullien, A. Voituriez, *Chem. Soc. Rev.* **2012**, *41*, 4884; b) S. I. Lee, N. Chatani, *Chem. Commun.* **2009**, 371; c) V. Michelet, P. Y. Toullec, J. P. Genet, *Angew. Chem.* **2008**, *120*, 4338; *Angew. Chem. Int. Ed.* **2008**, *47*, 4268.

[2] a) Platinum-catalyzed: F. Marion, J. Coulomb, C. Courillon, L. Fensterbank, M. Malacria, *Org. Lett.* **2004**, *6*, 1509; Gold-catalyzed: b) S. Couty, C. Meyer, J. Cossy, *Angew. Chem.* **2006**, *118*, 6878; *Angew. Chem. Int. Ed.* **2006**, *45*, 6726; Silver-catalyzed: c) P. Garcia, Y. Harrak, L. Diab, P. Cordier, C. Ollivier, V. Gandon, M. Malacria, L. Fensterbank, C. Aubert, *Org. Lett.* **2011**, *13*, 2952; d) For a cyclization of aryl ynamides, see: Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer, A. Davis, *Org. Lett.* **2005**, *7*, 1047.

[3] a) N. Saito, Y. Sato, M. Mori, *Org. Lett.* **2002**, *4*, 803; b) J. Huang, H. Xiong, R. P. Hsung, C. Rameshkumar, J. A. Mulder, T. P. Grebe, *Org. Lett.* **2002**, *4*, 2417; c) H. Wakamatsu, M. Sakagami, M. Hanata, M. Takeshita, M. Mori, *Macromol. Symp.* **2010**, *293*, 5.

[4] a) R. L. Greenaway, C. D. Campbell, O. T. Holton, C. A. Russell, E. A. Anderson, *Chem. Eur. J.* **2011**, *17*, 14366; b) R. L. Greenaway, C. D. Campbell, H. A. Chapman, E. A. Anderson, *Adv. Synth. Catal.* **2012**, *354*, 3187.

[5] For recent examples of reactions of ynamides, see: a) P. Huang, Z. Y. Chen, Q. Yang, Y. Y. Peng, *Org. Lett.* **2012**, *14*, 2790; b) K. A. DeKorver, X.-N. Wang, M. C. Walton, R. P. Hsung, *Org. Lett.* **2012**, *14*, 1768; c) D. L. Smith, W. R. F. Goundry, H. W. Lam, *Chem. Commun.* **2012**, *48*, 1505; d) R. B. Dateer, B. S. Shaibu, R.-S. Liu, *Angew. Chem.* **2012**, *124*, 117; *Angew. Chem. Int. Ed.* **2012**, *51*, 113; e) P. W. Davies, A. Cremonesi, L. Dumitrescu, *Angew. Chem.* **2011**, *123*, 9093; *Angew. Chem. Int. Ed.* **2011**, *50*, 8931; For recent examples of ynamides in [2+2+2] cyclization, see: f) N. Saito, T. Ichimaru, Y. Sato, *Org. Lett.* **2012**,

14, 1914; g) P. Garcia, Y. Evanno, P. George, M. Sevrin, G. Ricci, M. Malacria, C. Aubert, V. Gandon, *Chem. Eur. J.* **2012**, *18*, 4337; For reviews of ynamide chemistry, see: h) Y. Zhang, K. A. DeKorver, H. Y. Li, A. G. Lohse, R. Hayashi, Z. Lu, R. P. Hsung, *Chem. Rev.* **2010**, *110*, 5064; i) G. Evano, A. Coste, K. Jouvin, *Angew. Chem.* **2010**, *122*, 2902; *Angew. Chem. Int. Ed.* **2010**, *49*, 2840.

[6] For a review of catalytic selective synthesis, see: J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem.* **2012**, *124*, 11114; *Angew. Chem. Int. Ed.* **2012**, *51*, 10954.

[7] a) B. M. Trost, M. Lautens, *Tetrahedron Lett.* **1985**, *26*, 4887; b) B. M. Trost, M. Lautens, *J. Am. Chem. Soc.* **1985**, *107*, 1781; c) B. M. Trost, M. Lautens, C. Chan, D. J. Jebaratnam, T. Mueller, *J. Am. Chem. Soc.* **1991**, *113*, 636; d) B. M. Trost, G. J. Tanoury, M. Lautens, C. Chan, D. T. Macpherson, *J. Am. Chem. Soc.* **1994**, *116*, 4255; e) B. M. Trost, D. L. Romero, F. Rise, *J. Am. Chem. Soc.* **1994**, *116*, 4268; For reviews, see: f) B. M. Trost, *Chem. Eur. J.* **1998**, *4*, 2405; g) B. M. Trost, *Acc. Chem. Res.* **1990**, *23*, 34.

[8] For examples of enyne cycloisomerization using [Cp*Ru(cod)Cl], see: a) J. Le Paih, D. C. Rodriguez, S. Derien, P. H. Dixneuf, *Synlett* **2000**, 95; b) M. Mori, Y. Kozawa, M. Nishida, M. Kanamaru, K. Onozuka, M. Takimoto, *Org. Lett.* **2000**, *2*, 3245; For a single example of a ruthenium-catalyzed cyclization of an unsubstitued enynamide, requiring an ethene atmosphere, see: c) M. Mori, D. Tanaka, N. Saito, Y. Sato, *Organometallics* **2008**, *27*, 6313; d) N. Saito, D. Tanaka, M. Mori, Y. Sato, *Chem. Rec.* **2011**, *11*, 186; For ruthenium-catalyzed intermolecular coupling of ynamides with ethene, see: e) N. Saito, K. Saito, M. Shiro, Y. Sato, *Org. Lett.* **2011**, *13*, 2718; For a review of ruthenium-catalyzed processes, see: f) B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem.* **2005**, *117*, 6788; *Angew. Chem. Int. Ed.* **2005**, *44*, 6630.

[9] See the Supporting Information for details of substrate synthesis and assignment of stereochemistry by ^{1}H NMR nOe experiments.

[10] For examples of ruthenium-catalyzed formal [2+2] enyne cyclizations, see: a) N. Saito, Y. Tanaka, Y. Sato, *Org. Lett.* **2009**, *11*, 4124; b) A. Fürstner, A. Schlecker, C. W. Lehmann, *Chem. Commun.* **2007**, 4277; For pioneering work with norbornene, see: c) T. Mitsudo, K. Kokuryo, Y. Takegami, *J. Chem. Soc. Chem. Commun.* **1976**, 722; For a Pd-catalyzed formal [2+2] enyne cyclization, see: d) B. M. Trost, M. Yanai, K. Hoogsteen, *J. Am. Chem. Soc.* **1993**, *115*, 5294. Although these cyclobutenes could lead to 1,3-dienes by 4π-electrocyclic ring opening, we have found them to be resistant to this process.

[11] For a previous example of the contrasting behavior of palladium and ruthenium catalysts in enyne cycloisomerization, see: B. M. Trost, A. C. Gutierrez, E. M. Ferreira, *J. Am. Chem. Soc.* **2010**, *132*, 9206.

[12] For examples of intermolecular metal-catalyzed Ficini [2+2] cycloadditions of ynamides with electron-deficient alkenes, see: a) D. L. Smith, S. R. Chidipudi, W. R. Goundry, H. W. Lam, *Org. Lett.* **2012**, *14*, 4934; b) C. Schotes, A. Mezzetti, *Angew. Chem.* **2011**, *123*, 3128; *Angew. Chem. Int. Ed.* **2011**, *50*, 3072; c) H. Y. Li, R. P. Hsung, K. A. DeKorver, Y. G. Wei, *Org. Lett.* **2010**, *12*, 3780.

[13] B. M. Trost, J. Y. L. Chung, *J. Am. Chem. Soc.* **1985**, *107*, 4586.

[14] A minor amount of 1,5-diene was detected. For a similar observation, see Ref. [11].

[15] J. P. Michael, *Nat. Prod. Rep.* **2008**, *25*, 139.

[16] I. R. C. Bick, J. B. Bremner, N. W. Preston, I. C. Calder, *J. Chem. Soc. Chem. Commun.* **1971**, 1155.

[17] R. E. Beveridge, R. A. Batey, *Org. Lett.* **2012**, *14*, 540.

