ORGANIC
LETTERS

2011
Vol. 13, No. 18
4970–4973

Gold(I)-Catalyzed Tandem Cyclization–Selective Migration Reaction of 1,3-Dien-5-ynes: Regioselective Synthesis of Highly Substituted Benzenes

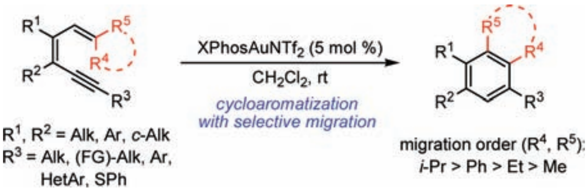
**Patricia García-García, Alberto Martínez, Ana M. Sanjuán,
Manuel A. Fernández-Rodríguez, and Roberto Sanz***

*Área de Química Orgánica, Departamento de Química, Facultad de Ciencias,
Universidad de Burgos, Pza. Misael Bañuelos s/n, 09001-Burgos, Spain*

rsd@ubu.es

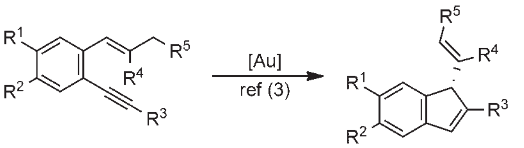
Received August 5, 2011

ABSTRACT

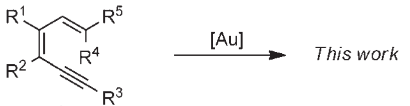


Highly substituted benzene derivatives have been easily prepared in a regioselective way from readily available 1,3-hexadien-5-ynes through a gold(I)-catalyzed tandem reaction. The process involves an initial cyclization followed by a selective Wagner–Meerwein shift in which the migration preference seems to be determined by the ability to stabilize a positive charge.

The transition-metal-catalyzed enyne cycloisomerization has become in the past decade a powerful strategy for the synthesis of functionalized cyclic structures.[1] In particular, gold complexes have shown a great ability to promote a wide variety of synthetically and mechanistically interesting transformations of polyunsaturated systems.[2] In this regard, we have recently reported a gold-catalyzed cycloisomerization of *o*-alkynylstyrenes that provides an easy enantioselective access to the indene skeleton (eq 1).[3] In this context, and in continuation of our ongoing work in gold-catalyzed transformations,[4] we became interested in the potential of related 1,3-dien-5-ynes **1** as precursors for gold(I)-catalyzed cycloisomerizations (eq 2).[5] If a reaction pathway analogous to that observed for *o*-alkynylstyrenes took place, highly substituted cyclopentadienes would be obtained. However, the fact that the central double bond is now not forming part of an aromatic ring could obviously play a definitive role in the reactivity giving rise to a completely different outcome.[6]



(1)



1

(2)

Whereas the thermal cycloaromatization of 1,3-hexadien-5-ynes to benzene derivatives (the "dihydro variant" of the Bergman cyclization also known as Hopf cyclization)

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(1) Selected recent revisions on transition-metal-catalyzed cycloisomerization reactions: (a) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268–4315. (b) Jiménez-Núñez, E.; Echavarren, A. *Chem. Rev.* **2008**, *108*, 3326–3350.

(2) Selected recent revisions on gold catalysis: (a) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221. (b) Shapiro, N. D.; Toste, F. D. *Synlett* **2010**, 675–691. (c) Das, A.; Sohel, S. M. A.; Liu, R.-S. *Org. Biomol. Chem.* **2010**, *8*, 960–979. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232–5241. (e) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994–2009. (f) Nolan, S. P. *Acc. Chem. Res.* **2011**, *44*, 91–100.

(3) Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem., Int. Ed.* **2010**, *49*, 4633–4637.

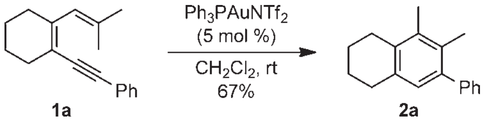
(4) (a) Sanz, R.; Miguel, D.; Rodríguez, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7354–7357. (b) Sanz, R.; Miguel, D.; Gohain, M.; García-García, P.; Fernández-Rodríguez, M. A.; González-Pérez, A.; Nieto-Faza, O.; de Lera, A. R.; Rodríguez, F. *Chem.—Eur. J.* **2010**, *16* 9818–9828.

10.1021/ol202129n

usually proceeds at > 200 °C,[7] their transition-metal-catalyzed cycloisomerization reactions have been scarcely explored. Some of the few reported examples are related to the ruthenium-catalyzed cycloaromatization of 1,3-dien-5-ynes having a terminal alkyne, which take place via vinylidene intermediates.[8] With 1-substituted 1,3-dien-5-ynes, Liu et al. have observed different reaction pathways depending on the substitution of the external olefin that mainly involve a [1,7]-hydrogen shift.[9] More recently, a mild gold-catalyzed cycloaromatization of related 2,4-dien-6-yne carboxylic acids has also been described.[10] Herein, we report a novel gold-catalyzed cycloaromatization of simple 1,3-dien-5-ynes **1** that takes place with a concurrent selective migration reaction.

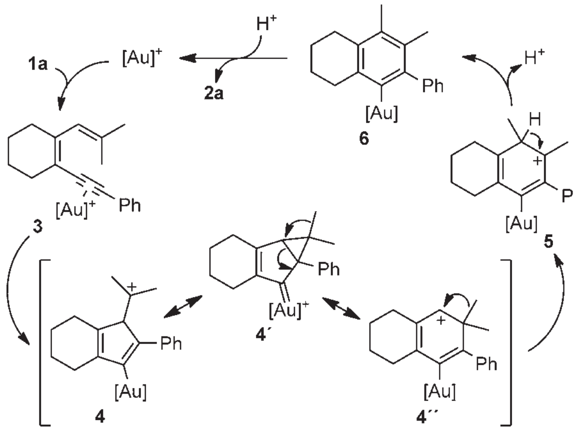
To our aim, we initially selected 1-(2-methylprop-1-enyl)-2-(2-phenylethynyl)-cyclohexene **1a** as a model substrate.[11] Although decomposition occurred when $AgSbF_6$ or $PtCl_2$ were used as catalysts, we were delighted to find that its reaction in dichloromethane at rt in the presence of catalytic amounts of $Ph_3PAuNTf_2$[12] gives rise to 1,2,3,4-tetrahydronaphthalene derivative **2a** as a single product that could be isolated in good yield (Scheme 1). The structure of **2a** was determined by NMR experiments and confirmed by X-ray diffraction analysis.[13]

Scheme 1. Initial Experiment: Cycloaromatization of **1a** to Tetrahydronaphthalene **2a**



The observed reaction pathway is clearly different from that previously observed in the cycloisomerization of related *o*-alkynylstyrenes (eq 1).[3] Moreover, although a cycloaromatization has taken place, as it had been earlier reported for analogous substrates using alternative catalysts,[8,9] the topology of the substituents in the final product notably differs from that described so far, thus accounting for a distinct reaction mechanism. More interestingly, it is worth pointing out that in this transformation one of the methyl groups initially bonded to the terminal olefin has formally migrated to an adjacent carbon in the final product.[14] A mechanism that could account for this cyclization–migration sequence is depicted in Scheme 2. The reaction would start with the coordination of the gold complex to the triple bond of the starting dienyne **1a** to give intermediate **3**. An intramolecular nucleophilic attack of the terminal olefin would lead to intermediate **4**. This intermediate could be represented as the contribution of several resonance structures (**4′**, **4″**, ...), delocalizing the positive charge along different positions of the molecule. Migration of one of the methyl groups in **4** would afford intermediate **5**. This migration could be explained either from **4″**, which would imply the transformation of a secondary carbocation into a more stable tertiary one (Wagner–Meerwein rearrangement), or from **4′** with a simultaneous opening of the cyclopropane ring. Finally, intermediate **5** would eliminate a proton to deliver aryl-gold compound **6** that after protodeauration affords the final product **2a**.

Scheme 2. Proposed Mechanism for the Formation of **2a** from **1a**: Tandem Cyclization–Migration Reaction



Noteworthy, in our previously reported cycloisomerization of related *o*-alkynylstyrenes we proposed a similar initial cyclization step, followed by a proton elimination from the corresponding intermediates analogous to **4** or **4′**, to explain the observed formation of indene derivatives.[3] Nevertheless, in the reaction of 1,3-dien-5-yne **1a** the proposed alternative reaction pathway *via* **4′** or **4″** could

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(5) For recent examples of Au-catalyzed cycloisomerizations of related 1,5-enynes, see: (a) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141–1144. (b) Kirsch, S. F.; Binder, J. T.; Crone, B.; Duschek, A.; Haug, T. T.; Lièbert, C.; Menz, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 2310–2313. (c) Horino, Y.; Yamamoto, T.; Ueda, K.; Kuroda, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131* 2809–2811.

(6) For an interesting example of selectivity switch by a small modification of the substrate, see: (a) Hashmi, A. S. K.; Rudolph, M.; Huck, J.; Frey, W.; Bats, J. W.; Hamzić, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 5848–5852.

(7) (a) Hopf, H.; Musso, H. *Angew. Chem., Int. Ed.* **1969**, *8*, 680. (b) For a review, see: Zimmermann, G. *Eur. J. Org. Chem.* **2001**, 457–471.

(8) (a) Merlic, C. A.; Pauly, M. E. *J. Am. Chem. Soc.* **1996**, *118*, 11319–11320. (b) Lian, J.-J.; Odedra, A.; Wu, C.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2005**, *127*, 4186–4187.

(9) Lian, J.-J.; Lin, C.-C.; Chang, H. K.; Chen, P.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 9661–9667.

(10) García-García, P.; Fernández-Rodríguez, M. A.; Aguilar, E. *Angew. Chem., Int. Ed.* **2009**, *48*, 5534–5537.

(11) For the preparation of starting dienynes **1**, **7**, and **9**, see Supporting Information.

(12) Mézailles, N.; Ricard, L.; Gagosz, F. *Org. Lett.* **2005**, *7* 4133–4136.

(13) CCDC 827051 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

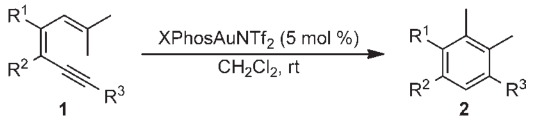
(14) (a) For a review on 1,2-alkyl migrations in reactions catalyzed by π-acids, see: Crone, B.; Kirsch, S. F. *Chem.—Eur. J.* **2008**, *14*, 3514–3522. (b) For a review on Cu-, Ag-, and Au-catalyzed migratory cycloisomerizations, see: Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Aldrichimica Acta* **2010**, *43*, 37–46.

be highly favored because now it involves an aromatization step, which is most probably the driving force of the whole process. It is also worth noting that whereas most of the reported 1,2-alkyl shifts in cascade Au-catalyzed reactions involve migration to an adjacent metal carbenoid center or a pinacol-type rearrangement,[14a] few examples have been described involving alternative pathways.[15]

Considering the novelty and interest of this transformation, as well as its potential application as a method for the regioselective synthesis of useful penta-substituted benzenes,[16] we decided to optimize the reaction conditions and test its scope. After checking several gold complexes,[17] we found out that the best conditions consisted in the use of 5 mol % of XphosAuNTf_2 (XPhos = 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl) in CH_2Cl_2 as solvent at rt, which allowed the formation of **2a** in 87% yield in a short reaction time of < 15 min. Under these optimized conditions a series of 1,3-dien-5-ynes **1** were reacted, and the results are shown in Table 1.[18]

Gratifyingly, the cyclization–migration sequence takes place in good yields for 1,3-dien-5-ynes **1a**–**g** bearing different substituents at the terminal position of the triple bond, including aromatic, heteroaromatic, alkenyl, cyclic, and functionalized alkyl, as well as heteroatomic, groups (Table 1, entries 1–6).[19] Moreover, regarding the substituent at the central double bond of the dienyne (R^1, R^2), the reaction tolerates both cyclic (entries 1–7) and linear (entry 8) aliphatic groups, as well as aromatic substituents (entries 9–10),[20] although a decrease in yield is observed when two aromatic substituents are present (entry 11).[21]

Table 1. Scope of the Gold-Catalyzed Rearrangement of 1,1-Dimethyl-1,3-hexadien-5-ynes **1**[a]



entry	1	R^1	R^2	R^3	2	yield (%)[b]
1	**1a**	$-(CH_2)_4-$		Ph	**2a**	87
2[c]	**1b**	$-(CH_2)_4-$		3-Th	**2b**	85
3	**1c**	$-(CH_2)_4-$		c-C_6H_9	**2c**	85
4	**1d**	$-(CH_2)_4-$		c-C_3H_5	**2d**	74
5	**1e**	$-(CH_2)_4-$		$(CH_2)_3CN$	**2e**	55
6	**1f**	$-(CH_2)_4-$		SPh	**2f**	83
7	**1g**	$-CH_2O(CH_2)_2-$		Ph	**2g**	76
8	**1h**	Et	Et	Ph	**2h**	86
9	**1i**	$-(CH_2)_2(o$-$C_6H_4)-$		Ph	**2i**	74[d]
10	**1j**	Me	Ph	Ph	**2j**	75[d]
11	**1k**	Ph	Ph	Ph	**2k**	50[e]

[a] Reactions stirred at rt for 30 min (complete consumption of the starting material was checked by GC-MS analysis). [b] Yield of isolated product based on the corresponding starting dienyne **1**. [c] Using $Ph_3PAuNTf_2$ as catalyst. [d] 10% of an isomeric side product was also isolated; see ref 20. [e] Lower yield was mostly due to decomposition under the reaction conditions. 3-Th = 3-thienyl, c-C_6H_9 = cyclohexenyl, c-C_3H_5 = cyclopropyl.

Next, taking into account the proposed mechanism that includes a migration step, we considered that dienynes **7** bearing a cyclic group at the terminal position of the olefin could be of great interest, because if they react in the same way as dienynes **1** their transformation would imply a ring expansion.[22] Therefore, we submitted several dienynes **7a**–**e** to the optimized reaction conditions and were delighted to find that, although some side reactions were observed for particular substrates, tricyclic compounds **8**, analogous to **2**, could be isolated in moderate to high yields (Table 2). Notably, not only five-membered rings were expanded to six-membered rings but also the more challenging expansion from a six-membered ring to a seven-membered ring was efficiently achieved, in a reaction that is compatible with different selected substituents in both the central olefin and the terminal position of the triple bond.

Finally, to check the selectivity of the migration step, we faced the reaction of dienynes **9**, which have two different substituents in the terminal position of the olefin, and therefore two groups that could potentially migrate (Table 3).[23] Pleasantly, a selective migration occurs in all cases, as determined by ^1H NMR of the crude product.[24] From the

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(15) (a) Dudnik, A. S.; Schwier, T.; Gevorgyan, V. *Org. Lett.* **2008**, *10*, 1465–1468. (b) Suárez-Pantinga, S.; Palomas, D.; Rubio, E.; González, J. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 7857–7861. (c) Davies, P. W.; Martin, N. *Org. Lett.* **2009**, *11*, 2293–2296. (d) Li, W.; Li, Y.; Zhang, J. *Chem.—Eur. J.* **2010**, *16*, 6447–6450.

(16) For transition-metal-catalyzed approaches to polysubstituted benzenes, see: (a) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901–2915. For recent examples of nonmetal-catalyzed syntheses of polyfunctionalized benzenes from 1,3-hexadien-5-ynes, see: (b) Matsumoto, S.; Takase, K.; Ogura, K. *J. Org. Chem.* **2008**, *73*, 1726–1731. (c) Zhou, H.; Xing, Y.; Yao, J.; Chen, J. *Org. Lett.* **2010**, *12*, 3674–3677. For other gold-catalyzed syntheses of benzene rings, see: (d) Hashmi, A. S. K.; Frost, T. M.; Bats, J. W. *J. Am. Chem. Soc.* **2000**, *122*, 11553–11554. (e) Dankwardt, J. W. *Tetrahedron Lett.* **2001**, *42*, 5809–5812. (f) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 411–414. (g) Hashmi, A. S. K.; Rudolph, M.; Siehl, H.-U.; Tanaka, M.; Bats, J. W.; Frey, W. *Chem.—Eur. J.* **2008**, *14*, 3703–3708.

(17) See Supporting Information for details.

(18) 1 mol % of XPhosAuNTf_2 was sufficient to cyclize model substrate **1a** (84% yield). However, no complete conversions were observed for some other substrates when using 1 mol % of catalyst.

(19) The corresponding terminal alkyne decomposed under the reaction conditions.

(20) For dienynes **1i** and **1j** an isomer of the expected product was also isolated in ~10% yield.

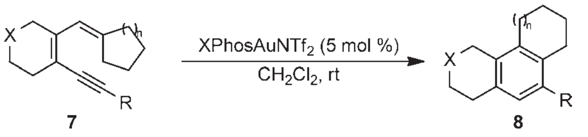
(21) For dienynes **1j** and **1k** it was observed that only the geometrical isomer with the stereochemistry shown in Table 1 (entries 10–11) reacted under the standard reaction conditions.

(22) Selected examples of gold-catalyzed ring expansions: (a) Gorin, D. J.; Davis, N. R.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 11260–11261. (b) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhauer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 5452–5455. (c) Lee, J. H.; Toste, F. D. *Angew. Chem., Int. Ed.* **2007**, *46*, 912–914. (d) Li, C. W.; Pati, K.; Lin, G.-Y.; Sohel, S. M. A.; Hung, H.-H.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2010**, *49*, 9891–9894.

(23) Selected examples of gold-catalyzed selective migrations: (a) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2007**, *46*, 5195–5197. (b) Hashmi, A. S. K.; Yang, W.; Rominger, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 5762–5765. See also ref 15. For Ru-catalyzed 1,2-halo and aryl shifts in the cycloisomerization of terminal *o*-(ethynyl)styrenes, see: (c) Shen, H.-C.; Pal, S.; Lian, J.-J.; Liu, R.-S. *J. Am. Chem. Soc.* **2003**, *125*, 15762–15763. See, also: Madhushaw, R. J.; Lo, C.-Y.; Hwang, C.-W.; Su, M.-D.; Shen, H.-C.; Pal, S.; Shaikh, I. R.; Liu, R.-S. *J. Am. Chem. Soc.* **2004**, *126*, 15560–15565.

(24) It was initially checked that both the *E* and *Z* isomers of the starting materials **9** showed analogous reactivity, and therefore, reactions were usually performed with a mixture of isomers.

Table 2. Tricyclic Compounds **8** by Gold-Catalyzed Cycloaromatization–Ring Expansion Sequence of Dienynes **7**[a]

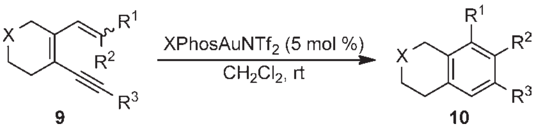


entry	**7**	R	X	*n*	**8**	yield (%)[b]
1	**7a**	Ph	CH_2	1	**8a**	62
2	**7b**	Ph	O	1	**8b**	60
3[c]	**7c**	Ph	CH_2	2	**8c**	80
4	**7d**	*c*-C_6H_9	CH_2	2	**8d**	81
5	**7e**	Ph	O	2	**8e**	76

[a] Reactions stirred at rt for 30 min (complete consumption of the starting material was checked by GC-MS analysis). [b] Yield of isolated product based on the corresponding starting dienyne **7**. [c] Reaction performed with $Ph_3PAuNTf_2$ as catalyst.

results (Table 3) we can determine the following migration aptitude order: ethyl migration selectively takes place over methyl migration (entry 1); for substrates bearing both an aliphatic and aromatic substituent, migration of the aromatic ring is preferred over methyl and ethyl migration (entries 2–3), whereas the isopropyl group selectively migrates over the phenyl group (entry 4).[25] Finally, in product **10e** (entry 5), which was obtained in moderate yield due to decomposition of the starting material under the reaction conditions,[26] formal migration of the hydrogen can be observed, although in this case the reaction could also be explained through a direct proton elimination from a **4''** type intermediate (Scheme 2). Therefore, the migration aptitude of the different substituents turns out to be *i*-Pr > Ph > Et > Me,[27] resembling the general order of likelihood of migration for the Baeyer–Villiger oxidation, and showing that the major factor in determining which group migrates seems to be the ability to accommodate partial positive charge. These results also demonstrate the compatibility of the reaction with the presence of an aromatic group in the terminal position of the olefin. In this sense, the high versatility of the reported transformation that allows variability in all the possible positions of the starting dienyne, together with the complete selectivity of the migration step, makes this reaction a useful methodology for the regioselective synthesis of pentasubstituted benzenes with up to five different substituents, as illustrated with examples **10f,g** (Table 3, entries 6–7).

Table 3. Tetrahydronaphthalene Derivatives **10** by Gold-Catalyzed Tandem Cyclization–Selective Migration Reactions of Dienynes **9**[a]



entry	**9**[b]	R^1	R^2	R^3	X	**10**	yield (%)[c]
1	**9a**	Et	Me	Ph	CH_2	**10a**	75
2	**9b**	Ph	Me	Ph	CH_2	**10b**	79
3	**9c**	Ph	Et	Ph	CH_2	**10c**	78
4	**9d**	*i*-Pr	Ph	Ph	CH_2	**10d**	72
5	**9e**	H	Ph	Ph	CH_2	**10e**	40
6	**9f**	Et	Me	3-Th	O	**10f**	62
7	**9g**	*i*-Pr	Ph	3-Th	O	**10g**	64

[a] Reactions stirred at rt for 30 min (complete consumption of the starting material was checked by GC-MS analysis). [b] Starting dienynes **9** were used as a mixture of geometrical isomers. [c] Yield of isolated product based on the corresponding starting dienyne **9**.

In conclusion, we have discovered that 1,1-disubstituted-1,3-hexadien-5-ynes react under gold-catalyzed conditions through an unprecedented tandem cyclization–migration sequence. Moreover, when two different groups can participate in the Wagner–Meerwein shift a complete selectivity was observed, which very roughly follows the order in which the groups are able to stabilize a positive charge. Further studies to prove the mechanism of this transformation and to extend its scope are currently in progress in our laboratory.

Acknowledgment. We are grateful to the Ministerio de Ciencia e Innovación (MICINN) and FEDER (CTQ2010-15358 and CTQ2009-09949/BQU) and Junta de Castilla y León (BU021A09 and GR-172) for financial suport. A.M. S. thanks Junta de Castilla y León for a predoctoral fellowship. P.G.-G. and M.A.F.-R. thank MICINN for "Juan de la Cierva" and "Ramón y Cajal" contracts. This paper is dedicated to Prof. Dr. Francisco J. Arnáiz on the occasion of his 65th birthday.

Supporting Information Available. Experimental procedures, characterization data for all new compounds, and crystallographic data (CIF). Copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The structure of the final products was determined based on NOESY experiments. See Supporting Information for details.

(26) A dienyne bearing only one methyl group at the terminal position of the olefin did not react under the reaction conditions and decomposed upon heating to 80 °C in DCE in the presence of XphosAuNTf$_2$ (5 mol %).

(27) An alternative mechanism involving skeletal rearrangements previous to the migration step, which could imply a reversed migratory aptitude, cannot be completely ruled out at this point.