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Central–axial–central chirality transfer: asymmetric synthesis of highly substituted indenes bearing a stereogenic quaternary carbon center from optically active propargyl alcohols†

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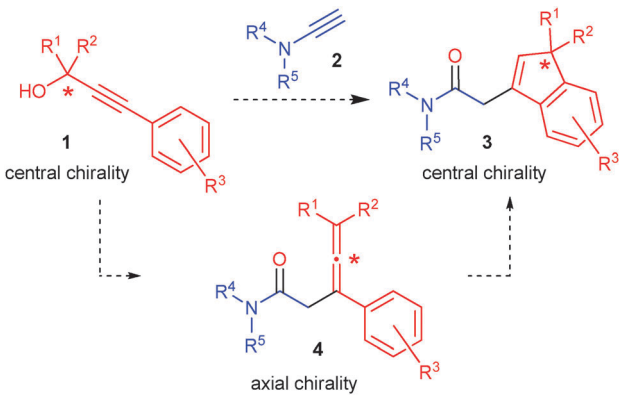
An asymmetric synthesis of highly substituted indenes 3, bearing a quaternary stereogenic carbon center, has been developed *via* the central–axial–central chirality transfer from optically active propargyl alcohols 1. This transformation involves the addition/rearrangement of 1 and ynamides 2 to give tetra-substituted allenes 4 and further cyclization of 4.

Indenes are important structural motifs, widely found in biologically active natural products and pharmaceutical drugs.[1] In addition, they serve as functional materials for electronics and optoelectronics[2] and as valuable ligands for transition metal complexes.[3] Consequently, organic chemists have focused on developing a number of synthetic routes towards indene derivatives.[4] Some representative methods include the carbocyclization of aryl-substituted propargyl alcohols or allyl alcohols,[5] the cyclization of aryl alkynes through sp^3 C–H activation,[6] the annulation of aryl allenes,[5c,e,g,7] the [3+2] annulation of alkynes with aryl carbonyl or imine compounds,[8] and the ring expansion of cyclopropanes or cyclopropenes bearing aryl groups.[9] Among these reports, however, only a few describe the synthesis of optically active indene derivatives, in particular, those bearing a quaternary stereogenic carbon center.[10]

We envisioned an asymmetric synthesis of highly substituted indene derivatives **3**, bearing a quaternary stereogenic carbon center, by a transformation of optically active aryl propargyl tertiary alcohols **1** and ynamides **2** (Scheme 1). The essential points of our transformation relied on the formation of optically active tetra-substituted allenes **4** and on the intramolecular cyclization of **4** into **3**, while maintaining the chiral integrity of **1** during the central–axial–central chirality transfer.[11] The asymmetric synthesis of indenes using optically active allenes has not been previously described. Although much effort has been devoted to the synthesis of allenes,[12] methods for supplying optically active tetra-substituted allenes are still largely limited.[13] This is ascribed to the lack of an efficient and general synthetic protocol for tetra-substituted allenes even in the racemic manner, and the facile racemization of optically active allenes in the presence of transition metals.[14,15] Here, we describe the studies of the transition metal-catalyzed conversion of propargyl alcohols **1** into tetra-substituted allenes **4** *via* the addition of **1** to ynamides **2** followed by the [3,3]-sigmatropic rearrangement of the intermediate propargyl vinyl ethers and the intramolecular cyclization of **4** to give highly substituted indenes **3**. This multistep reaction proceeds with the retention of chiral integrity of **1**.



Scheme 1 A strategy for the transformation of optically active propargyl alcohols **1** into highly substituted indenes **3**, bearing a quaternary stereogenic carbon center, *via* tetra-substituted allenes **4** with chirality transfer.

It is known that transition metal-induced π-activated triple bonds of ynamides undergo nucleophilic addition at the α-position of the nitrogen atom.[16] We hypothesized that sterically hindered tertiary propargyl alcohols **1** might add to ynamides **2** to *in situ* provide propargyl vinyl ethers **5**, which would serve as the precursor for the [3,3]-sigmatropic rearrangement. In addition, these two steps might proceed continuously at ambient temperature, in which the catalyst used for the nucleophilic addition could also promote the subsequent rearrangement into allenes **4**. In order

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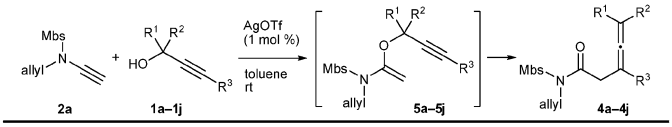
Table 1 Synthesis of tetra-substituted allenes **4a–4j** from **1a–1j** and **2a** in the presence of AgOTf

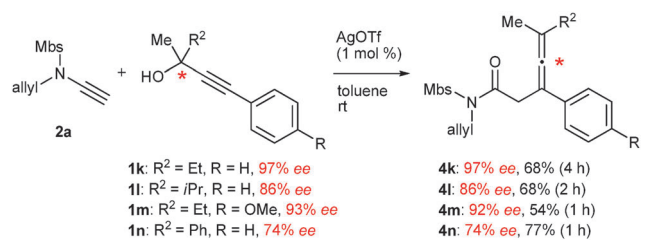


Entry	Substrate 1	R^1	R^2	R^3	Time (h)	Product 4	Yield[a] (%)
1	**1a**	Me	Me	Ph	1	**4a**	75 (38)[b]
2	**1b**	Me	Me	C_6H_4-4-OMe	2	**4b**	64
3	**1c**	Me	Me	C_6H_4-4-Cl	2	**4c**	70
4	**1d**	Me	CH_2OTBS	Ph	3	**4d**	83
5	**1e**	$(CH_2)_5$		Ph	1	**4e**	60
6[c]	**1f**	$CH_2OCMe_2OCH_2$		Ph	3	**4f**	77
7	**1g**	Me	Me	*N*-Boc-indol-5-yl	1	**4g**	58
8[d]	**1h**	Ph	Ph	Me	1	**4h**	55
9	**1i**	Et	Ph	Me	2.5	**4i**	73
10	**1j**	Me	Me	$(CH_2)_2Ph$	0.5	**4j**	59

Mbs = 4-methoxybenzenesulfonyl. [a] Yield of the isolated product. [b] Use of $(Ph_3P)AuOTf$, generated from $(Ph_3P)AuCl$ and AgOTf (1 mol% each), instead of AgOTf. [c] Further addition of AgOTf (1 mol%) and **2a** (1.2 equiv.) after 1 h. [d] Use of AgOTf (5 mol%).

to examine the feasibility of our hypothesis, the reaction of **1** with **2** was first investigated in either a prochiral or racemic form. Mixing **1a** and **2a**[17] in toluene at room temperature led to the recovery of starting materials. In the presence of highly alkynophilic $(Ph_3P)AuOTf$ (1 mol%), the addition of **1a** to **2a** proceeded smoothly at room temperature to directly afford tetra-substituted allene **4a** in 38% yield (Table 1, entry 1 in parentheses). We reasoned that the facile rearrangement of **5a** to **4a** could be ascribed to the high nucleophilicity of the amide enol moiety of **5a** and to the activation of a C–C triple bond in **5a** by the gold catalyst, which enhanced the electrophilicity of the acetylene. Screening of various catalysts[18] revealed AgOTf to be the most effective catalyst, which provided **4a** in 75% yield (entry 1). The substrate scope of the two-step cascade transformation was then investigated and it was found that various tertiary propargyl alcohols **1b–1j** (1.0 equiv.) react with **2a** (1.2 equiv.), in the presence of AgOTf (1 mol%), to provide tetra-substituted allenes **4b–4j** in good-to-excellent yields (entries 2–10). The reaction time required to reach completion was typically less than 3 h, and when R^3 was an aryl, a heteroaryl, or an alkyl group, the rearrangement proceeded. Notably, this method was compatible with acid-labile protecting groups such as OTBS, acetal, and Boc groups (entries 4, 6, and 7).

We next investigated the chirality transfer from optically active propargyl alcohols **1** into tetra-substituted allenes **4** (Scheme 2). Although transition metals often cause the (partial) racemization of optically active allenes,[14,15] we were pleased to find that the addition–rearrangement reactions of **1k–1n**[19] with **2a** underwent with the complete retention of the optical purities during the central-to-axial chirality transfer. We think that the key factor to suppress the racemization is the low affinity of silver catalysts for allenes and the small amount (1 mol%) of AgOTf used.[14b,20] To the best of our knowledge, this is the first example of the preparation of optically active tetra-substituted allenes by the [3,3]-sigmatropic rearrangement of propargyl vinyl ether derivatives.[14a,d,21]



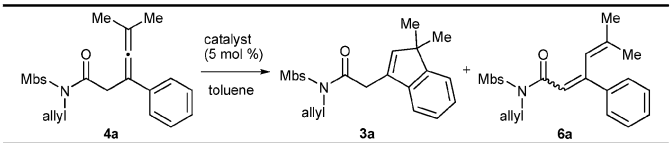
Scheme 2 Central-to-axial chirality transfer from optically active **1k–1n** to optically active **4k–4n**.

With tetra-substituted allenes **4** in hand, the intramolecular cyclization of **4** into indenes **3** became our next concern. As a model study, the conversion of **4a** into **3a** was investigated in toluene (Table 2). The AgOTf-catalyzed reaction of **4a**, either at room temperature or at 80 °C, did not give the desired product **3a** at all (entries 1 and 2). When $(Ph_3P)AuOTf$ (5 mol%) or $InCl_3$ (5 mol%) was used, the reaction led to the isomerization to produce the conjugate dienylamide **6a** as a main product (entries 3 and 4). It was found that **3a** could be obtained in good yield when $PtCl_2$ was employed (entry 5).[22] In addition, the choice of the solvent proved to have a significant influence on the ratio of **3a** and **6a**, and THF afforded **3a** in quantitative yield and complete selectivity (entry 6), while toluene, CH_2Cl_2, and DMF resulted in the formation of mixtures of **3a** and **6a**.

The optimized reaction conditions were applicable to the synthesis of a wide range of highly substituted indenes **3**, as shown in Scheme 3. In particular, sterically demanding products (**3d**, **3e**, and **3l**) were obtained in high yields, albeit longer reaction times were required. The intramolecular cyclization of indole derivative **4g** took place exclusively at the C4 position to give **3g**, and in the cases of **4h** and **4i**, where R^2 = phenyl, the cyclization occurred at the allene moiety, forming indenes **3h** and **3i**, respectively, with the acetamide group at the C1 position.

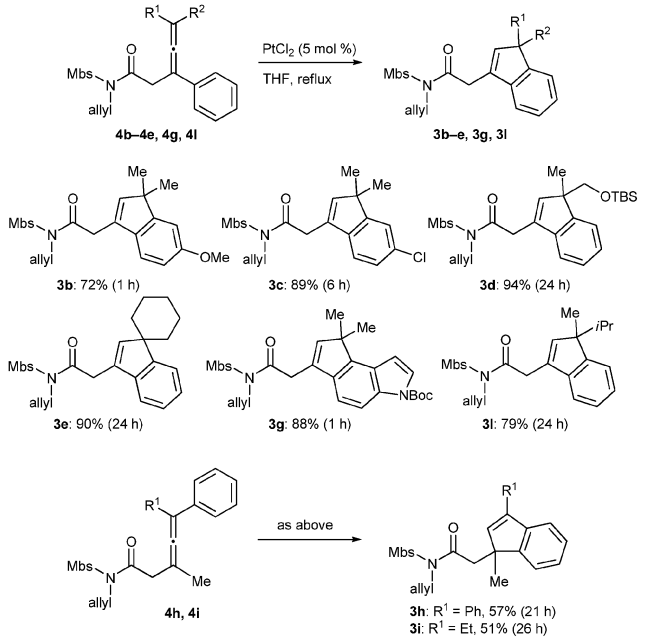
Having established the basic study, we finally undertook an intramolecular cyclization of enantioenriched allenes **4** (Scheme 4). Although electron-rich allenes are prone to the

Table 2 Catalyst screening for the intramolecular cyclization of tetra-substituted allene **4a**

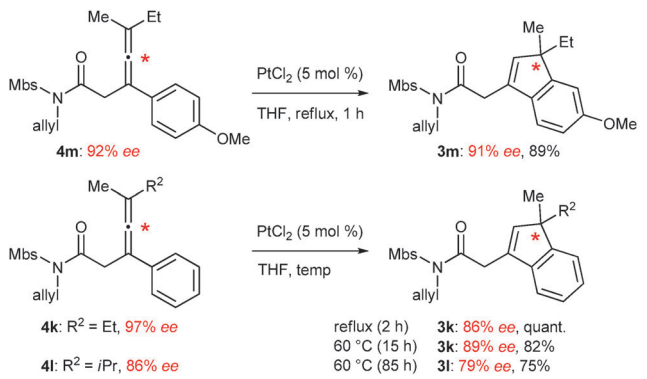


Entry	Catalyst	Temp. (°C)	Time (h)	**3a**[a] (%)	**6a**[a] (%)
1	AgOTf	rt	12	0	0
2	AgOTf	80	12	0	9
3	$(Ph_3P)AuOTf$[b]	rt	1	0	100
4	$InCl_3$	50	4	Trace	83
5	$PtCl_2$	80	1	73	9
6[c]	$PtCl_2$	Reflux	1	100 (98)[d]	0

[a] NMR yield using 1,4-dimethoxybenzene as the internal standard. [b] Generated from $(Ph_3P)AuCl$ and AgOTf (5 mol% each). [c] The reaction was performed in THF. [d] Yield of the isolated product is shown in parentheses.



Scheme 3 Pt-catalyzed intramolecular cyclization of **4** into highly substituted indenes **3**.



Scheme 4 Axial-to-central chirality transfer from allenes **4m**, **4k**, and **4l**.

transition metal-catalyzed racemization,[14b,15c] we were pleased to find out that the transformation of **4m** (92% ee), having an electron-rich aryl group, occurred with the complete transfer of its axial chirality to the newly formed quaternary stereogenic carbon center in **3m**. The cyclization of **4k** (97% ee) produced indene **3k** quantitatively, with 86% ee.[23] Reducing the reaction temperature to 60 °C slightly improved the optical purity of **3k** (89% ee). The little loss of the optical purity may be due to a platinum-catalyzed racemization of allene prior to the cyclization. In the case of **4l**, having a sterically demanding isopropyl group, a high level of chirality transfer was achieved, albeit the reaction time was longer.

In summary, we have reported a new, convenient, and environmentally benign route for synthesising a variety of highly substituted indene derivatives **3** bearing a quaternary stereogenic carbon center. The reaction occurs between tertiary propargyl alcohols **1** and ynamide **2a**, and for the first time, the central chirality of **1** was effectively transferred into that of **3**. This was achieved *via* the temporary formation of tetrasubstituted allenes **4** by the central–axial–central chirality transfer. Moreover, our method provides a new synthetic route towards the less accessible racemic and optically active tetrasubstituted allenes. Additional investigation to determine the absolute stereochemistries of **4** and **3** and a practical extension of this method are currently in progress.

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Notes and references

1 (*a*) G. Majetich and J. M. Shimkus, *J. Nat. Prod.*, 2010, **73**, 284; (*b*) B.-F. Li, W. J. Moree, J. Yu, T. Coon, S. Zamani-Kord, S. Malany, K. Jalali, J. Wen, H. Wang, C. Yang, S. R. J. Hoare, R. E. Petroski, A. Madan, P. D. Crowe and G. Beaton, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2629; (*c*) E. Alcalde, N. Mesquida, J. Frigola, S. López-Pérez and R. Mercè, *Org. Biomol. Chem.*, 2008, **6**, 3795; (*d*) D.-C. Oh, P. G. Williams, C. A. Kauffman, P. R. Jensen and W. Fenical, *Org. Lett.*, 2006, **8**, 1021; (*e*) Y. Wang, S.-Y. Mo, S.-J. Wang, S. Li, Y.-C. Yang and J.-G. Shi, *Org. Lett.*, 2005, **7**, 1675.

2 (*a*) L. Liu, Y. Fan, Q. He, Y. Zhang, D. Zhang-Negrerie, J. Huang, Y. Du and K. Zhao, *J. Org. Chem.*, 2012, **77**, 3997; (*b*) X. Zhu, C. Mitsui, H. Tsuji and E. Nakamura, *J. Am. Chem. Soc.*, 2009, **131**, 13596; (*c*) J. Yang, M. V. Lakshmikantham, M. P. Cava, D. Lorcy and J. R. Bethelot, *J. Org. Chem.*, 2000, **65**, 6739.

3 (*a*) B. Wang, *Coord. Chem. Rev.*, 2006, **250**, 242; (*b*) H. G. Alt and A. Köppl, *Chem. Rev.*, 2000, **100**, 1205.

4 For selected recent examples, see: (*a*) X.-Y. Shi and C.-J. Li, *Org. Lett.*, 2013, **15**, 1476; (*b*) K. B. S. Magar and Y. R. Lee, *Org. Lett.*, 2013, **15**, 4288; (*c*) X. Jia, D. A. Petrone and M. Lautens, *Angew. Chem., Int. Ed.*, 2012, **51**, 9870; (*d*) A. S. K. Hashmi, I. Braun, P. Nösel, J. Schädlich, M. Wieteck, M. Rudolph and F. Rominger, *Angew. Chem., Int. Ed.*, 2012, **51**, 4456; (*e*) F. Zhou, X. Han and X. Lu, *J. Org. Chem.*, 2011, **76**, 1491; (*f*) C.-R. Liu, F.-L. Yang, Y.-Z. Jin, X.-T. Ma, D.-J. Cheng, N. Li and S.-K. Tian, *Org. Lett.*, 2010, **12**, 3832.

5 For the synthesis of indenes from propargyl alcohols, see: (*a*) J. Zhao and D. A. Clark, *Org. Lett.*, 2012, **14**, 1668; (*b*) K. V. Sajna and K. C. Kumara Swamy, *J. Org. Chem.*, 2012, **77**, 5345; (*c*) P. N. Chatterjee and S. Roy, *J. Org. Chem.*, 2010, **75**, 4413; (*d*) S. Wang, Y. Zhu, Y. Wang and P. Lu, *Org. Lett.*, 2009, **11**, 2615; (*e*) X. Zhang, W. T. Teo and P. W. H. Chan, *Org. Lett.*, 2009, **11**, 4990; (*f*) W. Huang, P. Zheng, Z. Zhang, R. Liu, Z. Chen and X. Zhou, *J. Org. Chem.*, 2008, **73**, 6845; (*g*) N. Marion, S. Díez-González, P. de Frémont, A. R. Noble and S. P. Nolan, *Angew. Chem., Int. Ed.*, 2006, **45**, 3647. For the use of allyl alcohols as a substrate, see: (*h*) J. Panteleev, R. Y. Huang, E. K. J. Lui and M. Lautens, *Org. Lett.*, 2011, **13**, 5314; (*i*) S. Guo and Y. Liu, *Org. Biomol. Chem.*, 2008, **6**, 2064.

6 (*a*) S. Yang, Z. Li, X. Jian and C. He, *Angew. Chem., Int. Ed.*, 2009, **48**, 3999; (*b*) M. Tobisu, H. Nakai and N. Chatani, *J. Org. Chem.*, 2009, **74**, 5471.

7 (*a*) B. Meng and S. Ma, *Org. Lett.*, 2012, **14**, 2674; (*b*) C.-R. Liu, T.-T. Wang, Q.-B. Qi and S.-K. Tian, *Chem. Commun.*, 2012, **48**, 10913; (*c*) M. Asikainen and S. Woodward, *Tetrahedron*, 2012, **68**, 5492; (*d*) Z.-X. Ma, S. He, W. Song and R. P. Hsung, *Org. Lett.*, 2012, **14**, 5736; (*e*) S. Yamazaki, Y. Yamamoto, Y. Fukushima, M. Takebayashi, T. Ukai and Y. Mikata, *J. Org. Chem.*, 2010, **75**, 5216; (*f*) G.-Y. Lin, C.-Y. Yang and R.-S. Liu, *J. Org. Chem.*, 2007, **72**, 6753.

8 (*a*) K. Muralirajan, K. Parthasarathy and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2011, **50**, 4169; (*b*) F. W. Patureau, T. Besset, N. Kuhl and F. Glorius, *J. Am. Chem. Soc.*, 2011, **133**, 2154; (*c*) E. J. Park, S. H. Kim and S. Chang, *J. Am. Chem. Soc.*, 2008, **130**, 17268; (*d*) Y. Kuninobu, Y. Tokunaga, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 202.

9 (*a*) B. Hu, S. Xing and Z. Wang, *Org. Lett.*, 2008, **10**, 5481; (*b*) Z.-B. Zhu and M. Shi, *Chem. – Eur. J.*, 2008, **14**, 10219; (*c*) V. K. Yadav, N. V. Kumar and M. Parvez, *Chem. Commun.*, 2007, 2281.

10 For the asymmetric synthesis of enantioenriched indenes bearing quaternary stereogenic carbon centers, see: (*a*) Z. Chai and T. J. Rainey, *J. Am. Chem. Soc.*, 2012, **134**, 3615; (*b*) W. Rao, M. J. Koh, P. Kothandaraman and P. W. H. Chan, *J. Am. Chem. Soc.*, 2012, **134**, 10811; (*c*) D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 11098. For other asymmetric synthesis of indenes, see: (*d*) A. Martínez, P. García-García, M. A. Fernández-Rodríguez, F. Rodríguez and R. Sanz, *Angew. Chem., Int. Ed.*, 2010, **49**, 4633; (*e*) J. A. Brekan, T. E. Reynolds and K. A. Scheidt, *J. Am. Chem. Soc.*, 2010, **132**, 1472; (*f*) F. Zhou, M. Yang and X. Lu, *Org. Lett.*, 2009, **11**, 1405; (*g*) P. Dubé and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 12062; (*h*) R. Shintani, K. Okamoto and T. Hayashi, *Chem. Lett.*, 2005, **34**, 1294.

11 D. Campolo, S. Gastaldi, C. Roussel, M. P. Bertrand and M. Nechab, *Chem. Soc. Rev.*, 2013, **42**, 8434.

12 For selected reviews, see: (*a*) S. Yu and S. Ma, *Chem. Commun.*, 2011, **47**, 5384; (*b*) M. Ogasawara, *Tetrahedron: Asymmetry*, 2009, **20**, 259; (*c*) K. M. Brummond and J. E. DeForrest, *Synthesis*, 2007, 795.

13 (*a*) T. Hashimoto, K. Sakata, F. Tamakuni, M. J. Dutton and K. Maruoka, *Nat. Chem.*, 2013, **5**, 240; (*b*) B. M. Partridge, L. Chausset-Boissarie, M. Burns, A. P. Pulis and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2012, **51**, 11795; (*c*) Z. Li, V. Boyarskikh, J. H. Hansen, J. Autschbach, D. G. Musaev and H. M. L. Davies, *J. Am. Chem. Soc.*, 2012, **134**, 15497; (*d*) T. Miura, M. Shimada, S.-Y. Ku, T. Tamai and M. Murakami, *Angew. Chem., Int. Ed.*, 2007, **46**, 7101.

14 (*a*) D. Wang, L. N. S. Gautam, C. Bollinger, A. Harris, M. Li and X. Shi, *Org. Lett.*, 2011, **13**, 2618; (*b*) V. K.-Y. Lo, C.-Y. Zhou, M.-K. Wong and C.-M. Che, *Chem. Commun.*, 2010, **46**, 213; (*c*) B. Trillo, F. López, S. Montserrat, G. Ujaque, L. Castedo, A. Lledós and J. L. Mascareñas, *Chem. – Eur. J.*, 2009, **15**, 3336; (*d*) B. D. Sherry and F. D. Toste, *J. Am. Chem. Soc.*, 2004, **126**, 15978; (*e*) A. Horváth and J.-E. Bäckvall, *Chem. Commun.*, 2004, 964; (*f*) A. Claesson and L.-I. Olsson, *J. Chem. Soc., Chem. Commun.*, 1979, 524.

15 The transition-metal-catalyzed reaction of optically active allenes frequently causes the (partial) racemization, see: (*a*) H. Liu, D. Leow, K.-W. Huang and C.-H. Tan, *J. Am. Chem. Soc.*, 2009, **131**, 7212; (*b*) J. H. Lee and F. D. Toste, *Angew. Chem., Int. Ed.*, 2007, **46**, 912; (*c*) C. Deutsch, B. Gockel, A. Hoffmann-Röder and N. Krause, *Synlett*, 2007, 1790; (*d*) Z. Liu, A. S. Wasmuth and S. G. Nelson, *J. Am. Chem. Soc.*, 2006, **128**, 10352.

16 G. Evano, A. Coste and K. Jouvin, *Angew. Chem., Int. Ed.*, 2010, **49**, 2840.

17 Various ynamides were screened in the AgOTf-catalyzed reaction with **1a**, and **2a** gave the best results. For details, see ESI†.

18 For additional catalysts examined, such as gold, silver, and ruthenium compounds, see ESI†.

19 (*a*) V. J. Forrat, O. Prieto, D. J. Ramón and M. Yus, *Chem. – Eur. J.*, 2006, **12**, 4431; (*b*) L. Liu, R. Wang, Y.-F. Kang, H.-Q. Cai and C. Chen, *Synlett*, 2006, 1245.

20 N. Kern, A. Blanc, S. Miaskiewicz, M. Robinette, J.-M. Weibel and P. Pale, *J. Org. Chem.*, 2012, **77**, 4323 and references cited therein.

21 (*a*) Z.-B. Zhu and S. F. Kirsch, *Chem. Commun.*, 2013, **49**, 2272; (*b*) D. V. Vidhani, M. E. Krafft and I. V. Alabugin, *Org. Lett.*, 2013, **15**, 4462; (*c*) T. Cao, J. Deitch, E. C. Linton and M. C. Kozlowski, *Angew. Chem., Int. Ed.*, 2012, **51**, 2448; (*d*) O. F. Jeker and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3474; (*e*) C. Wang, W. Zhao, H. Li and L. Guo, *Green Chem.*, 2009, **11**, 843; (*f*) M. O. Frederick, R. P. Hsung, R. H. Lambeth, J. A. Mulder and M. R. Tracey, *Org. Lett.*, 2003, **5**, 2663.

22 Although a one-pot transformation from **1a** to **3a** by the use of a catalytic amount of $PtCl_2$ should be more attractive, some trials on the application of $PtCl_2$ for the reaction of **1a** and **2a** resulted in failure (for details, see ESI†).

23 Reducing the reaction time (0.5 h) produced a 1.8 : 1 mixture of **3k** (91% ee) and recovered **4k** (88% ee), suggesting that the platinum-catalyzed racemization of **4k** gradually took place prior to its intramolecular cyclization.

