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Enantioselective Rhodium-Catalyzed Synthesis of α-Chloromethylene-γ-Butyrolactams from *N*-Allylic Alkynamides

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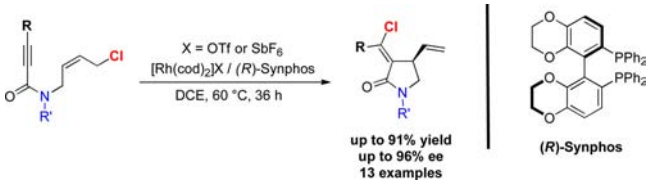
ABSTRACT



The first enantioselective cycloisomerization with intramolecular halogen migration of various 1,6-enynes promoted by a cationic Rh-Synphos catalyst is reported. This method provides an efficient route to enantiomerically enriched γ-butyrolactam derivatives, which are important core scaffolds found in numerous natural products and biologically active molecules. Good yields and enantiomeric excesses up to 96% are achieved.

Ring systems abound in natural products and biologically active molecules, among which γ-butyrolactam structures are of preeminent importance since they are widely spread in medicinal chemistry.[1] Therefore, the development of efficient methods for the stereoselective synthesis of these relevant targets appears to be highly desirable. The metal-catalyzed cycloisomerization[2] reaction is an atom-economical, challenging transformation for the rearrangement of polyunsaturated compounds to cyclic derivatives. Although cycloisomerization of 1,*n*-enynes has found widespread use owing to the development of efficient catalytic systems for the synthesis of carbo- and heterocycles,[3] only a few examples of Pd-catalyzed cyclization reactions

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(1) (a) Nilsson, B. M.; Ringdahl, B.; Hacksell, U. *J. Med. Chem.* **1990**, *33*, 580. (b) Bergmann, R.; Gericke, R. *J. Med. Chem.* **1990**, *33*, 492. (c) Qiao, L.; Wang, G.; George, C.; Lewin, N. E.; Blumberg, P. M.; Kozikowski, A. P. *J. Am. Chem. Soc.* **1998**, *120*, 6629. (d) Feling, R. H.; Buchanan, G. O.; Mincer, T. J.; Kauffman, C. A.; Jensen, P. R.; Fenical, W. *Angew. Chem., Int. Ed.* **2003**, *42*, 355. (e) Manan, R. R.; Teisan, S.; White, D. J.; Nicholson, B.; Grodberg, J.; Neuteboom, S. T. C.; Lam, K. S.; Mosca, D. A.; Lloyd, G. K.; Potts, B. C. M. *J. Nat. Prod.* **2005**, *68*, 240. (f) Ng, P. Y.; Tang, Y.; Knosp, W. M.; Stadler, H. S.; Shaw, J. T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5352. (g) Fenical, W.; Jensen, P. R.; Palladino, M. A.; Lam, K. S.; Lloyd, G. K.; Potts, B. C. *Bioorg. Med. Chem.* **2009**, *17*, 2175.

(2) (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (b) Lloyd-Jones, G. C. *Org. Biomol. Chem.* **2003**, *1*, 215. (c) Fairlamb, I. J. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 1048. (d) Nieto-Oberhuber, C.; Lopez, S.; Jiménez-Nunez, E.; Echavarren, A. M. *Chem.—Eur. J.* **2006**, *12*, 5916. (e) Zhang, L.; Sun, J.; Kozmin, S. A. *Adv. Synth. Catal.* **2006**, *348*, 2271. (f) Chianese, A. R.; Lee, S. J.; Gagne, M. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4042. (g) Michelet, V.; Toullec, P. Y.; Genet, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. (h) Lee, S. I.; Chatani, N. *Chem. Commun.* **2009**, 371. (i) Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075. (j) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208. (k) Soriano, E.; Marco-Contelles, J. *Acc. Chem. Res.* **2009**, *42*, 1026. (l) Pradal, A.; Toullec, P. Y.; Michelet, V. *Synthesis* **2011**, 1501. (m) Aubert, C.; Fensterbank, L.; Garcia, P.; Malacria, M.; Simonneau, A. *Chem. Rev.* **2011**, *111*, 1954. (n) Marinetti, A.; Jullien, H.; Voituriez, A. *Chem. Soc. Rev.* **2012**, *41*, 4884.

(3) (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Trost, B. M. *Chem.—Eur. J.* **1998**, *4*, 2405. (c) Trost, B. M.; Toste, D. *J. Am. Chem. Soc.* **2000**, *122*, 714. (d) Sturla, S. J.; Kabalaeui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976 and references therein. (e) Trost, B. M.; Lee, D. C.; Rise, F. *Tetrahedron Lett.* **1989**, *30*, 651. (f) Trost, B. M.; Czeskis, B. A. *Tetrahedron Lett.* **1994**, *35*, 211. (g) Goeke, A.; Sawamura, M.; Kuwano, R.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 662. (h) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

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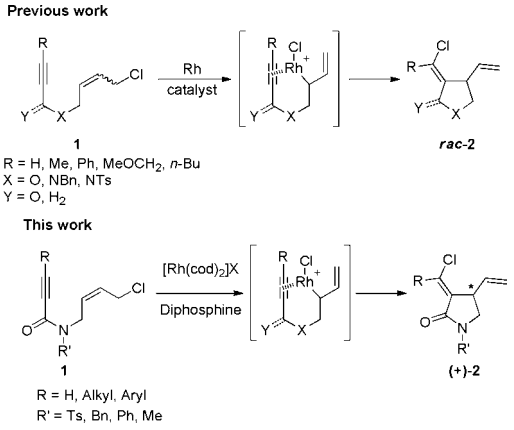
of 1,6-enynes to racemic α-halomethylene-γ-butyrolactones and lactams have been reported, including our own work.[4] Zhang et al. first reported the cycloisomerization of 1,6-enynes promoted by a rhodium catalyst for the synthesis of both racemic and enantioenriched γ-butyrolactones with excellent yields and regio- and enantioselectivities.[5] In this context, we were interested in the rhodium-catalyzed cyclization of 1,6-enynes with a halogen atom at the allylic position through a π-allyl or *enyl* ($\sigma + \pi$) rhodium intermediate.[6] The resulting exocyclic vinyl-chlorine structure would be suitable to undergo further cross-coupling reactions and provides useful functionalized heterocyclic compounds.

Scheme 1. 1,6-Enyne Cyclization with Halogen Migration



Since, in these cyclization reactions, a stereogenic center is generated in the product **2** from a planar sp^2-carbon in the starting material **1**, we envisaged the development of an asymmetric version of these cycloisomerization reactions using a combination of chiral diphosphine ligands and rhodium complexes. We report herein the first enantioselective Rh-catalyzed construction of α-chloromethylene-γ-butyrolactams from *N*-tethered 1,6-enynes through cycloisomerization with intramolecular halogen migration (Scheme 1).

In our initial work on cyclization of alkynoates, we demonstrated that the Rh(I)-*rac*-BINAP complex exhibited high activity in this cycloisomerization reaction.[6b] Therefore, we screened a number of chiral C_2-symmetric atropisomeric diphosphine ligands **L1**−**L8** that were commercially available or developed in our laboratories (Table 1).

Initial investigations began with the cycloisomerization of **1a** as a standard substrate using 20 mol % of catalyst, prepared *in situ* from $[Rh(COD)_2]^+X^-$ with various diphosphines at 50 °C in $ClCH_2CH_2Cl$ for 24 h. In most of the cases, the α-chloromethylene-γ-butyrolactam product **2a** was isolated in good to excellent yields and selectivities.

Examination of the results listed in Table 1 clearly showed that the stereochemical outcome of the reaction depended on the structure of the ligand considered. When the reaction was carried out using (*R*)-Binap (**L1**),[7] the cyclized product **2a** was obtained in 93% isolated yield and with an encouraging enantiomeric excess of 81% (Table 1, entry 1). To our delight, the (*R*)-Synphos ligand (**L2**)[8] exhibited extremely high catalytic activity for the cycloisomerization of **1a**, providing **2a** in 91% yield and with an excellent ee of 96% (Table 1, entry 2). The use of the (*S*)-Difluorphos (**L3**),[9] (*S*)-Segphos (**L4**),[10] and (*S*)-Sunphos (**L5**)[11] diphosphines, possessing a similar dihedral angle but different electronic character, gave good enantioselectivities ranging from 86 to 91%. These results indicate that the electronic feature of the ligand has no significant influence on the enantioselectivity (Table 1, entries 3−5). In sharp contrast, the steric properties of the diphosphine ligand, in particular the aryl substituents at the phosphorus atom, play a crucial role in the stereochemical outcome of the reaction, as outlined in Table 1.

This steric effect was revealed by comparison of the selectivity of the reaction conducted with catalysts bearing the Sunphos family of ligands (Table 1, entries 5−8). The unsubstituted diphenyl Sunphos **L5** and the corresponding 4-Me-C_6H_4 substituted diphosphine **L6** afforded **2a**, in good to excellent yields with comparable selectivities (Table 1, entries 5−6, 86 and 87% ee, respectively), while much lower ee's were observed with ligands **L7** and **L8**, which possess bulky aryl moieties on the phosphorus (Table 1, entries 7 and 8, 59 and 33% ee, respectively). Based on the above results, we found that (*R*)-Synphos was well suited for the cycloisomerization reaction. The nature

(4) (a) Ma, S.; Lu, X. *J. Chem. Soc., Chem. Commun.* **1990**, 733. (b) Ma, S.; Lu, X. *Org. Chem.* **1991**, *56*, 5120. (c) Ma, S.; Lu, X. *J. Org. Chem.* **1993**, *58*, 1245. (d) Zhu, G.; Zhang, Z. *J. Org. Chem.* **2005**, *70*, 3339.

(5) (a) Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2000**, *122*, 6490. (b) Cao, P.; Zhang, X. *Angew. Chem., Int. Ed.* **2000**, *39*, 4104. (c) Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 3457. (d) Lei, A.; Waldkirch, J. P.; He, M.; Zhang, X. *Angew. Chem., Int. Ed.* **2002**, *41*, 4526. (e) Lei, A.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 8198.

(6) (a) Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2003**, *125*, 6370. (b) Tong, X.; Li, D.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 7601. (c) Wang, J.; Xie, X.; Ma, F.; Peng, Z.; Zhang, L.; Zhang, Z. *Tetrahedron* **2010**, *66*, 4212.

(7) Miyashita, A.; Yasuda, A.; Takaya, H.; Toriumi, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 7932.

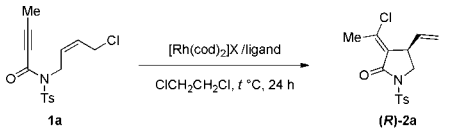
(8) (a) Duprat de Paule, S.; Champion, N.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Dellis, P. WO Patent 03029259, 2003. (b) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Eur. J. Org. Chem.* **2003**, 1931. (c) Duprat de Paule, S.; Jeulin, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Deschaux, G.; Dellis, P. *Org. Process Res. Dev.* **2003**, *7*, 399. (d) Jeulin, S.; Ayad, T.; Ratovelomanana-Vidal, V.; Genet, J.-P. *Adv. Synth. Catal.* **2007**, *349*, 1592. (e) Pautigny, C.; Jeulin, S.; Ayad, T; Zhang, Z.; Genet, J.-P.; Ratovelomanana-Vidal, V. *Adv. Synth. Catal.* **2008**, *350*, 2525. (f) Pautigny, C.; Debouit, C.; Vayron, P.; Ayad, T.; Ratovelomanana-Vidal, V. *Tetrahedron: Asymmetry* **2010**, *21*, 1382. (g) Wu, Z.; Ayad, T.; Ratovelomanana-Vidal, V. *Org. Lett.* **2011**, *13*, 3782.

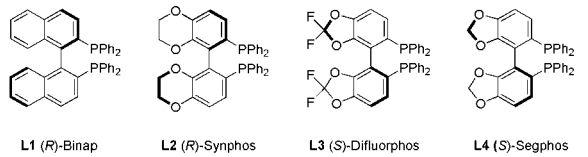
(9) (a) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 320. (b) Jeulin, S.; Duprat de Paule, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799.

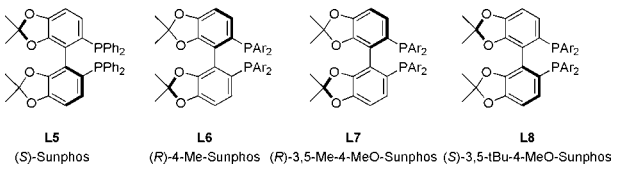
(10) Saito, T.; Yokozawa, T.; Ishizaki, T.; Moroi, T.; Sayo, N.; Miura, T.; Kumobayashi, H. *Adv. Synth. Catal.* **2001**, *343*, 264.

(11) (a) Sun, Y.; Wan, X.; Guo, M.; Wang, D.; Dong, X.; Pan, Y.; Zhang, Z. *Tetrahedron: Asymmetry* **2004**, *15*, 2185. (b) Meng, Q.; Sun, Y.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Zhang, Z. *J. Org. Chem.* **2008**, *73*, 3842. (c) Tao, X.; Li, W.; Ma, X.; Li, X.; Fan, W.; Xie, X.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z. *J. Org. Chem.* **2012**, *77*, 612. (d) Ma, X.; Li, W.; Li, X.; Tao, X.; Fan, W.; Xie, X.; Ayad, T.; Ratovelomanana-Vidal, V.; Zhang, Z. *Chem. Commun.* **2012**, *48*, 5352.

Table 1. Optimization of the Reaction Conditions[a]







entry	ligand	X	Rh catalyst (mol %)	yield (%)[b]	ee (%)[c]
1	**L1**	SbF_6	20	93	81 (*R*)
2	**L2**	SbF_6	20	91	96 (*R*)
3	**L3**	SbF_6	20	84	87 (*S*)
4	**L4**	SbF_6	20	87	91 (*S*)
5	**L5**	SbF_6	20	77	86 (*S*)
6	**L6**	SbF_6	20	95	87 (*R*)
7	**L7**	SbF_6	20	75	59 (*R*)
8	**L8**	SbF_6	20	39	33 (*S*)
9	**L2**	PF_6	20	89	96 (*R*)
10	**L2**	OTf	20	90	96 (*R*)
11	**L2**	OTf	15[d]	90	96 (*R*)
12	**L2**	OTf	10[d]	70	96 (*R*)
13	**L2**	OTf	5[e]	55	93 (*R*)
14	**L2**	SbF_6	15[d]	91	96 (*R*)

[a] All reactions were performed using 0.2 mmol of substrate **1a** with x mol % of Rh-catalyst, 1.1 x mol % of ligand in 2 mL of $ClCH_2CH_2Cl$. [b] After flash chromatography. [c] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) or by HPLC analysis. Absolute configuration was determined to be (*R*) by X-ray crystallographic analysis. [d] Reaction run at 60 °C for 36 h. [e] Reaction run at 70 °C for 36 h.

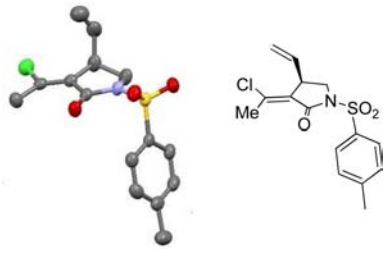
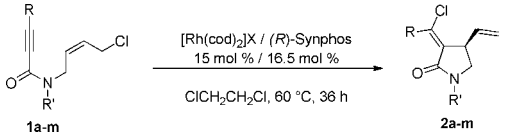
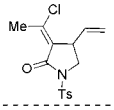
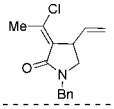
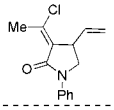
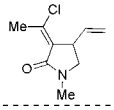
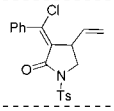
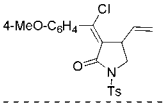
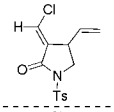
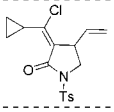
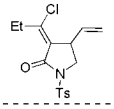
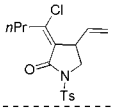
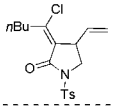
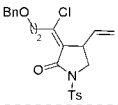
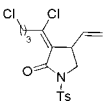


Figure 1. Structure determination for compound (+)-**2a** by X-ray crystallographic analysis.

of the noncoordinant counteranion did not seem to influence the catalytic activity or the enantioselectivity, as

Table 2. Rh-Synphos-Catalyzed Cycloisomerization Reaction[a]



entry		product	X	yield (%)[b]	ee (%)[c]
1	**2a**		SbF_6	91	96 (*R*)
2	**2b**		OTf	48	67 (*R*)
3	**2c**		OTf	51	72 (*R*)
4	**2d**		SbF_6	45	77 (*R*)
5	**2e**		SbF_6	44[d]	50 (*S*)[e]
6	**2f**		OTf	35[d]	50 (*R*)
7	**2g**		OTf	63	53 (*R*)
8	**2h**		OTf	35[d]	70 (*R*)
9	**2i**		SbF_6	64	91 (*R*)
10	**2j**		SbF_6	67	88 (*R*)
11	**2k**		OTf	65	86 (*R*)
12	**2l**		SbF_6	51	88 (*R*)
13	**2m**		SbF_6	68	88 (*R*)

[a] All reactions were performed using 0.2 mmol of substrate **1** with 15 mol % of Rh-catalyst, 16.5 mol % of ligand in 2 mL of $ClCH_2CH_2Cl$. [b] After flash chromatography. [c] Determined by chiral stationary phase-supercritical fluid chromatography (CSP-SFC) or by HPLC analysis. Absolute configuration was determined to be (*R*) by X-ray crystallographic analysis of **2a**; the configurations of the other products were then assigned by analogy. [d] Determined by ^1H NMR analysis. [e] (*S*)-Segphos was used.

similar results were obtained with different Rh precatalysts. Replacement of $[Rh(cod)_2]^+SbF_6^-$ by either $[Rh(cod)_2]^+PF_6^-$ or $[Rh(cod)_2]^+OTf^-$ provided **2a** with similar yields and enantioselectivities (Table 1, compare entry 2 vs entries 9 and 10). Interestingly, the catalyst loading could be reduced from 20% to 15% or 10% without affecting the stereochemical integrity of the new stereogenic center, although the reaction had to be conducted at 60 °C for 36 h to reach completion (Table 1, entries 11, 12, and 14). Finally, attempts to decrease the catalyst loading further to 5 mol % gave rise to the desired product **2a** with lower yield and selectivity (Table 1, entry 13, 55% yield, 93% ee). The absolute configuration of the α-chloromethylene-γ-butyrolactam product **2a** was unambiguously established to be (*R*) based on a single-crystal X-ray crystallographic analysis (Figure 1).[12]

Next, we evaluated the scope of this transformation. Toward this end, several *N*-tethered 1,6-enyne derivatives (**1a**−**m**) were prepared according to known procedures and subsequently cycloisomerized under our optimized reaction conditions using either $[Rh(cod)_2]^+SbF_6^-$ or $[Rh(cod)_2]^+OTf^-$ as rhodium sources. As shown in Table 2, both reactivity and enantioselectivity were influenced by the nature of the *N*-protecting group. Indeed, when comparing the results obtained with the *N*-tosyl derivative **1a**, reaction of enynes **1b**−**d** bearing a benzyl, phenyl, and methyl group provides the desired products **2b**−**d** in significantly lower yields and enantioselectivities (Table 2, compare entry 1 vs entries 2−4, 45 to 51% yield, 67 to 77% ee). The data of Table 2 also show that this asymmetric C−C bond-forming reaction is highly substrate-dependent.

A lower catalytic activity in terms of both reactivity and selectivity was obtained with enyne substrates **1e**−**f** bearing an aromatic ring on the acetylenic terminal moiety (Table 2, entries 5 and 6, 35 to 44% yield, 50% ee). A similarly moderate enantioselectivity of 53% was obtained with the nonsubstituted *N*-allylic alkynamide **1g** (R = H), albeit with a better isolated yield of 63% (Table 2, entry 7). A significantly better enantiofacial discrimination was reached for the cyclopropyl derivative **1h** (Table 2, entry 8, 70% ee), but this result was still considerably lower than the one obtained with compound **1a** (Table 2, compare entry 1 vs 8). A further demonstration of this substrate dependence was illustrated by the cycloisomerization of enyne substrates **1i**−**m** bearing an alkyl group on the acetylenic terminal moiety. Pleasingly, good catalytic activity can be restored when R is an ethyl, *n*-propyl, or *n*-butyl group, providing the desired products **2i**−**k** in good yields and selectivities (Table 2, entries 9−11, 64 to 67% yield, 86 to 91% ee). Furthermore, functionalized enynes **1l**−**m** with benzyloxy and chlorine atom substituents proved to be suitable substrates for this transformation, affording compounds **2l**−**m** with higher enantioselectivities than those obtained with **2j**−**k** (Table 2, entries 12 and 13, 51 to 68% yield, 88% ee).

In summary, we have developed an unprecedented enantioselective rhodium-catalyzed cycloisomerization of *N*-tethered 1,6-enynes with an intramolecular halogen shift leading to the corresponding α-chloromethylene-γ-butyrolactams in moderate to high isolated yields (up to 91%) and with good to excellent enantioselectivities (up to 96%). The functional group tolerance and substrate scope reported here have not been demonstrated for any other intramolecular halogen shift migration asymmetric cycloisomerization reaction to date. On the other hand, our useful cycloisomerization reaction can access functionalized enantiomerically enriched α-chloromethylene-γ-butyrolactams that are difficult to obtain otherwise. Further studies on expanding the substrate scope and exploring the synthetic utility of this reaction are currently underway in our laboratories.

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Supporting Information Available. Detailed experimental procedures and spectroscopic data for new compounds (^1H, ^{13}C NMR, SFC/HPLC spectra) and the crystallographic information file (CIF) for compound (*R*)-**2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) See Supporting Information. CCDC 885687 contains the supplementary crystallographic data for this paper. These data for compound (*R*)-**2a** can be obtained free of charge from The Cambridge Crystallography Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

The authors declare no competing financial interest.