

Gold(I)-Catalyzed Domino Cyclizations of Diynes for the Synthesis of Functionalized Cyclohexenone Derivatives. Total Synthesis of (–)-Gabosine H and (–)-6-*epi*-Gabosine H

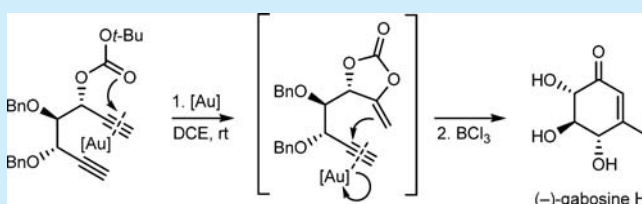
Bojan Vulovic,^{*,†} Dusan Kolarski,[†] Filip Bihelovic,^{*,†} Radomir Matovic,[‡] Maja Gruden,[†] and Radomir N. Saicic^{*,†}

[†]Faculty of Chemistry, University of Belgrade, Studentski trg 16, P.O. Box 51, 11158 Belgrade, Serbia

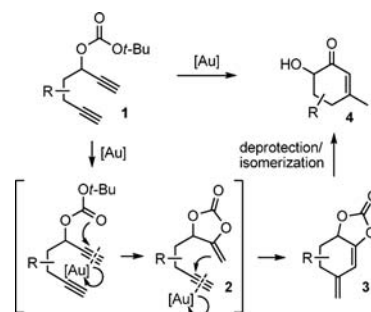
[‡]ICTM Center for Chemistry, Njegoseva 12, 11000 Belgrade, Serbia

S Supporting Information

ABSTRACT: 1,6-Diynes with a *t*-butylcarbonate group in the propargylic position undergo gold(I)-catalyzed domino-cyclization which affords α -hydroxycyclohexenones. The described sequence can be applied on functionalized, highly oxygenated substrates, as exemplified in the synthesis of (–)-gabosine H and its epimer.



Scheme 1. Principle of Au(I)-Catalyzed Domino Cyclization of 1,6-Diynes



Reducing the number of synthetic steps, as well as the time and effort associated with workup procedures, minimizing the use of solvents, and maximizing the atom economy of the process remain constant challenges in organic synthesis. These issues can be simultaneously addressed by use of domino reactions,¹ which allow for rapid increase of molecular complexity in a single synthetic step. Reactions catalyzed by gold complexes are particularly well suited for sequencing, as the rich organogold chemistry involves a number of reactive intermediates (carbocations, carbenes, or organometallics) and the possibility of a mechanistic crossover.² Gold complexes are best known for their ability to trigger addition reactions to alkynes.³ This property was exploited in the design of domino sequences, which convert substrates with suitably positioned unsaturated moieties into cyclic structures.

Some time ago, Gagosz and Buzas reported the gold(I)-catalyzed cyclization of propargyl *tert*-butyl carbonates to cyclic carbonates.⁴ We envisaged an extension of this reaction into a tandem cyclization that would eventually provide α -hydroxycyclohexenone derivatives.⁵ The blueprint of the transformation is represented in Scheme 1. The starting compound would be 1,6-diyne of type 1, and the sequence would start as previously described to give a cyclic enol carbonate 2 which should then undergo the second 6-*exo*-cyclization with the formation of a carbon–carbon bond. The expected product of the overall reaction would be bicyclic diene 3, a latent form of a thermodynamically more stable α -hydroxycyclohexenone 4.

The feasibility of this concept was tested on diyne 1a as a conformationally flexible, Thorpe–Ingold effect-free substrate. In the first experiment, diyne 1a was treated with 5 mol % of Ph₃PAuNTf₂ catalyst, at rt, in dichloromethane solution, which resulted in quantitative conversion into cyclic carbonate of type 2a (within 30 min). However, increasing the temperature to 50 °C promoted a second reaction that was complete within 4 h and afforded cyclohexenone derivative 4a in 55% yield. Optimization

of the reaction conditions included screening of the solvent (THF, DCM, DCE, MeCN, PhMe, DMF), ligand (PPh₃, P(C₆F₅)₃, XPhos, JohnPhos, tri-*o*-furylphosphine, tris(2,6-di-*t*-Bu-phenyl) phosphite), and additives (AgBF₄, AgSbF₆, AgPF₆, MeSO₃H, MS 4 Å). We found that the catalytic cocktail involving 5 mol % of JohnPhosAuCl procatalyst with 20 mol % of AgSbF₆ in DCE allows the domino cyclization to be accomplished at rt.

A series of 1,6-diynes 1a–i were then prepared and submitted to the optimized reaction conditions. The results of these experiments are presented in Table 1. In most examples, the desired cyclohexenone derivatives were obtained in moderate/good yields. Both secondary (entries 1, 5, 6, and 7) and tertiary (entries 4, 8, and 9) propargylic carbonates can be used. Unfortunately, the reaction did not work with nonterminal alkynes (entries 2 and 3). Notably, no isomerization/aromatization of hydroxycyclohexenones into the corresponding phenols (their thermodynamically more stable redox equiv-

Received: June 30, 2016

Published: July 26, 2016

Table 1. Gold(I)-Catalyzed Domino Cyclizations of 1,6-Diynes

entry	substrate	product	yield (%)
1			55 ^a
2			0
3			96 ^a
4			62
5			67
6			47 ^c
7			47
8			68
9			85

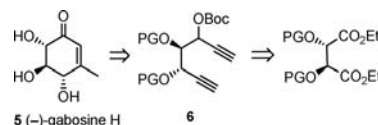
^aPh₃PAuNTf₂ was used as a catalyst. ^bJohnPhosAu(MeCN)SbF₆ was used as a catalyst at 55 °C.

alents) was observed under the reaction conditions. The corresponding 1,5- and 1,7-diynes did not yield any cycloalkenone derivatives, indicating that the 5-*exo*- and 7-*exo*-cyclization as a second step are not feasible. The reactions of diastereoisomeric diynes **1h** and **1i** are worthy of note from a stereochemical viewpoint: whereas compound **1h** gave stereochemically pure *cis* product **4h** (entry 8), the diastereoisomeric substrate **1i** produced a mixture of *cis*/*trans* decalones in **4h** (*cis*):**4i** (*trans*) = 1.8:1 ratio (entry 9). This could be explained by a reversible Meyer–Schuster rearrangement of compound **1i**, where the equilibration of the tertiary stereogenic center in **4i** is effected via the corresponding allene.

Gold complexes are both carbo- and oxophilic. Therefore, we wondered whether the described reaction sequence would tolerate a relatively high level of functionalization of precursors and thus be suitable for syntheses of highly oxygenated cyclohexenone derivatives. We decided to test the synthetic applicability of this domino reaction in the total synthesis of gabosines. When this research was underway,⁶ Li, Luo, Yang, and collaborators reported the sequential cyclization of 1,7-diynes leading to *exo*-methylene cyclohexene derivatives and applied it in an elegant synthesis of a series of drimane sesquiterpenoids.⁷ Later on, this principle was exploited in a very efficient enantioselective synthesis of the cladiellin family of natural products.⁸

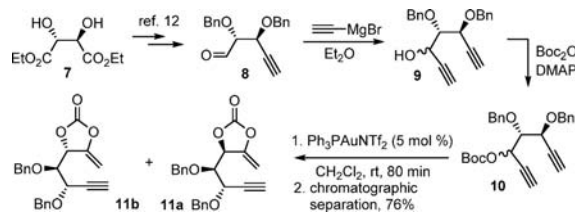
Gabosines are secondary metabolites of *Streptomyces* strains. Since the initial isolation of the first compound of the class,⁹ the

number of family members has steadily increased. Although they have shown modest biological activity so far, these carbasugar-type molecules have attracted considerable interest from synthetic organic chemists, and the subject has been recently reviewed.¹⁰ Gabosine H (**5**) was previously synthesized by Prasad and Kumar.¹¹ Our approach to the synthesis of this compound is outlined in Scheme 2. According to this plan, the

Scheme 2. Retrosynthetic Analysis of Gabosine H (**5**)

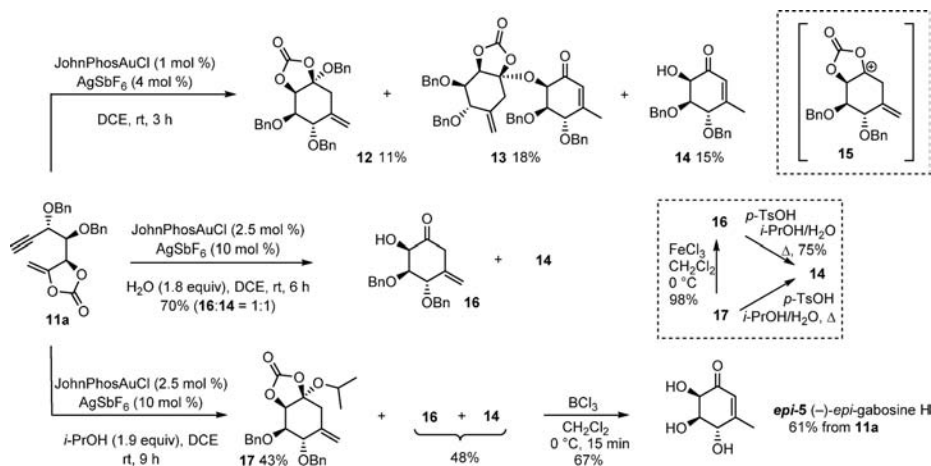
trihydroxycyclohexenone framework should be directly assembled from the corresponding diyne **6**; this chiral synthon should be derived from D-(−)-tartaric acid.

The synthesis of the cyclization precursors was accomplished as represented in Scheme 3. The known aldehyde **8** was obtained

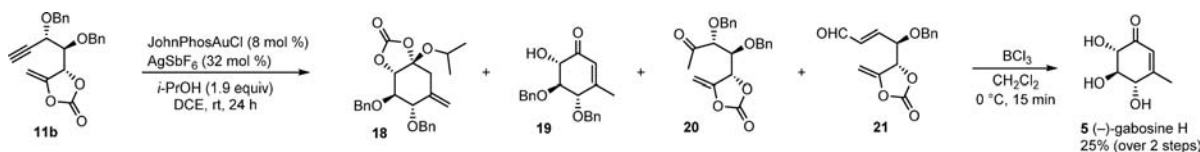
Scheme 3. Synthesis of the Cyclization Precursors **11a** and **11b**

from D-(−)-diethyl tartrate (38% over seven steps).¹² The conversion of aldehyde **8** into propargylic alcohol **9** was effected by acetylide addition. This reaction was performed according to several experimental protocols¹³ but, unfortunately, with an unsatisfactory stereochemical outcome: either an equimolar mixture of diastereoisomers was obtained or the undesired isomer (leading to gabosine H epimer) predominated. Unstable diynes **9** were not isolated but converted into the corresponding Boc derivatives **10**. These latter two compounds were inseparable; therefore, they were converted into diastereoisomeric enol carbonates **11a** and **11b** and separated by column chromatography.

The cyclization was first attempted with diastereoisomer **11a**, leading to *epi*-gabosine H (*epi*-**5**; Scheme 4). Upon exposure to the previously established conditions, **11a** gave a mixture of three compounds, **12**, **13**, and **14**, in 44% combined yield. All three compounds were the products of 6-*exo*-cyclization, with differences in the functionalization pattern. Whereas enone **14** was the expected product of the cyclization/isomerization/hydrolysis sequence, the other two (i.e., **12** and **13**) were acetals: apparently, the reaction proceeds via a cabocationic intermediate **15**, which can be intercepted by the product **14** (to give acetal **13**) but which is reactive enough to break the etheral C–O bond and pluck the oxygen nucleophile from the product **14** (or the substrate **11a**) to give acetal **12**. To suppress this side reaction, we performed the cyclization in the presence of water as an external nucleophile: to our pleasure, a mixture of cyclohexenones **16** and **14** was obtained in 70% combined yield. Remarkably, the cyclization was faster than the gold-catalyzed hydration of alkyne. Compound **16** could be converted into conjugated enone **14** on treatment with a hot aqueous solution of

Scheme 4. Cyclization of 11a and Synthesis of (–)-*epi*-Gabosine H (*epi*-5)

Scheme 5. Cyclization of 11b and Synthesis of (–)-Gabosine H (5)



p-TsOH in *i*-PrOH. An even higher yield of synthetically useful intermediates was obtained when the reaction was performed in the presence of 2-propanol: in this case, the mixture of cyclic products 17, 16, and 14 was obtained in 91% combined yield. This mixture was not separated, or hydrolyzed, but directly treated with BCl₃ to give (–)-*epi*-gabosine H (*epi*-5) in 67% yield. It should be noted that acetal 17 could be selectively converted into either cyclohexenone 16 or 14.

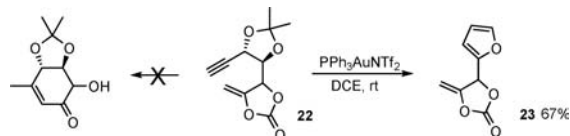
The cyclization of the second diastereoisomer (11b), leading to gabosine H (5), was found to be more difficult. Whereas the cyclization of 11a was complete within 9 h, the conversion of 11b under the similar conditions required 3 days and produced a mixture of four products (Scheme 5). By analogy with the former protocol, the reaction mixture was not separated but directly submitted to deprotection with BCl₃. In this case, the required product, (–)-gabosine H (5), was obtained in 25% overall yield. A more detailed analysis of the reaction mixture showed that the desired products (i.e., 18 and 19) were accompanied by ketone 20 and enal 21 (in quantities of up to 30% each). Apparently, slow cyclization and the long reaction time gave rise to the side reaction, hydration of the triple bond of the substrate 11b. Thus, whereas this synthetic study showed that the gold-catalyzed domino cyclization of 1,6-diyne can be successfully applied to highly functionalized, oxygenated substrates, it also indicated that the stereochemical aspects can have an important effect on the efficiency of the cyclization. The proper choice of the protecting groups is also important, as shown in Scheme 6: when the cyclization was attempted with enol carbonate 22 (dioxolane

protecting group, instead of benzyl ethers) the product of reaction was furan 23 (for the proposed mechanism of this transformation, see the SI). This example shows that gold(I) complexes can induce deprotection, or anchimeric assistance, of suitably positioned protecting groups via transient carbocationic species.

We believe that, in the cyclization reaction, gold(I) complex acts as a carbophilic π -acid and that the reaction proceeds via a carbocationic intermediate of type 15, as confirmed by the interception of this intermediate by external nucleophile, such as 2-propanol. However, reactions on structurally related systems have been shown in the literature to involve carbene intermediates and gold acetylides.^{4,5d,e,14} In order to test the possible intermediacy of these species, DFT calculations were performed on the model systems. Our results clearly indicate the dominant role of mononuclear gold species, with more than double reaction barriers in comparison to the dinuclear complexes (Figure S1 and Table S1). A detailed study of the gold-catalyzed enyne cycloisomerization reaction on mononuclear complexes (Figure 1) shows that cycloisomerization from a chairlike transition state (TS 1) leads to a structure that can be described as a gold-coordinated carbocation intermediate (Int 1), while boatlike and cyclopropanoid TSs (TS 2 and TS 3) form almost identical gold-stabilized singlet carbene intermediates (Int 2 and Int 3). The energy difference between both activation energies and intermediate products of model systems is sufficient to assert that the gold-carbocation intermediate is predominant and governs the proposed reaction mechanism.

To summarize, a gold(I)-catalyzed domino cyclization of 1,6-diynes offers an efficient access to 6-hydroxycyclohexenones. The reaction sequence can be applied on highly oxygenated systems, as shown in the syntheses of (–)-gabosine H and 6-*epi*-(–)-gabosine H.

Scheme 6. Cyclization of a Dioxolane-Protected Substrate 22 into Furan 23



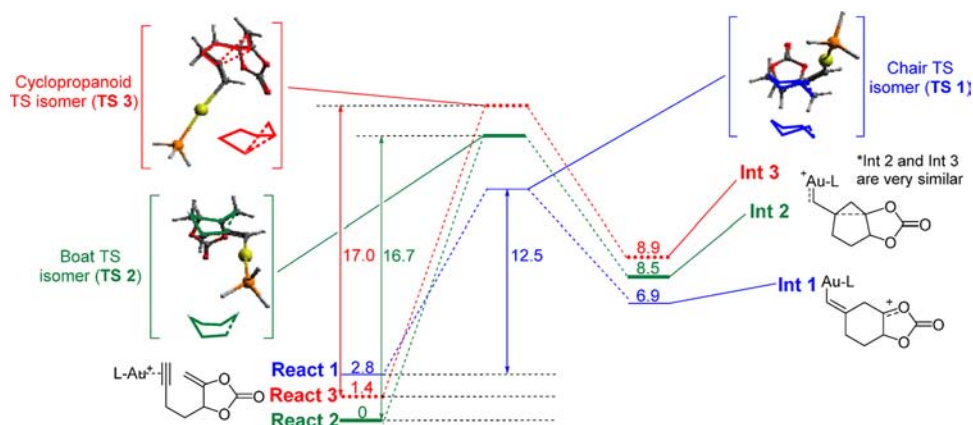


Figure 1. Calculated geometries and transition states for the enyne cycloisomerization step. Gibbs free energies (in kcal/mol), obtained using M06/TZ2P level of theory, are given relative to the React 2 (products and reactants), while the barriers are given relative to the appropriate reactant structure.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01898.

Experimental procedures; spectral data and NMR spectra for all compounds; mechanistic explanation of the reaction shown in Scheme 6 (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: bvulovic@chem.bg.ac.rs.

*E-mail: filip@chem.bg.ac.rs.

*E-mail: rsaicic@chem.bg.ac.rs.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Serbian Ministry of Education, Science and Technological Development (Project No. 172027) and by the Serbian Academy of Sciences and Arts (Project No. F193). We acknowledge the support of the FP7 RegPot project FCUB ERA GA No. 256716. The EC does not share responsibility for the content of the article.

■ REFERENCES

- (1) For the most recent book and review articles, see: (a) *Domino Reactions: Concepts for Efficient Organic Synthesis*; Tietze, L. F., Ed.; Wiley-VCH: Singapore, 2014. (b) Ardkhean, R.; Caputo, D. F. J.; Morrow, S. M.; Shi, H.; Xiong, Y.; Anderson, E. A. *Chem. Soc. Rev.* **2016**, 45, 1557–1569. (c) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, 114, 2390–2431. (d) Pellissier, H. *Chem. Rev.* **2013**, 113, 442–524. (e) Clavier, H.; Pellissier, H. *Adv. Synth. Catal.* **2012**, 354, 3347–3403.
- (2) For the most recent books and selected reviews, see: (a) *Gold Catalysis. An Homogeneous Approach*; Toste, F. D., Michelet, V., Eds.; Imperial College Press: Singapore, 2014; Catalytic Science Series, Vol. 13. (b) Gagosz, F. Golden Opportunities in the Synthesis of Natural Products and Biologically Active Compounds. In *Modern Tools for the Synthesis of Complex Bioactive Molecules*; Cossy, J., Arseniyadis, S., Eds.; Wiley & Sons Inc., 2012; pp 111–154. (c) Pflästerer, D.; Hashmi, S. K. *Chem. Soc. Rev.* **2016**, 45, 1331–1367. (d) Fürstner, A. *Acc. Chem. Res.* **2014**, 47, 925–938. (e) Ranieri, B.; Escofet, I.; Echavarren, A. E. *Org. Biomol. Chem.* **2015**, 13, 7103–7118. (f) Wang, Y.-M.; Lackner, A. D.; Toste, F. D. *Acc. Chem. Res.* **2014**, 47, 889–901.

- (3) (a) Dorel, R.; Echavarren, A. *Chem. Rev.* **2015**, 115, 9028–9072. (b) Fensterbank, L.; Malacria, M. *Acc. Chem. Res.* **2014**, 47, 953–965.
- (4) (a) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Tetrahedron* **2009**, 65, 1889–1901. (b) Buzas, A. K.; Gagosz, F. *Org. Lett.* **2006**, 8, 515–518.
- (5) For selected examples of reactions of structurally related substrates that give another type of products, see: (a) Lim, C.; Kang, J.-E.; Lee, J.-E.; Shin, S. *Org. Lett.* **2007**, 9, 3539–3542. (b) Barabé, F.; Levesque, P.; Korobkov, I.; Barriault, L. *Org. Lett.* **2011**, 13, 5580–5583. (c) Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem., Int. Ed.* **2012**, 51, 6181–6186. (d) Chen, Y.; Chen, M.; Liu, Y. *Angew. Chem., Int. Ed.* **2012**, 51, 6493–6497. (e) Rao, W.; Koh, M. J.; Li, D.; Hirao, H.; Chan, P. W. H. *J. Am. Chem. Soc.* **2013**, 135, 7926–7932. (f) Lauterbach, T.; Gatzweiler, S.; Nösel, P.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2013**, 355, 2481–2487. (g) Yan, J.; Tay, G. L.; Neo, C.; Lee, B. R.; Chan, P. W. H. *Org. Lett.* **2015**, 17, 4176–4179. (h) Wildermuth, R.; Speck, K.; Magauer, T. *Synthesis* **2016**, 48, 1814–1824.
- (6) Kolarski, D. Diploma Work, Faculty of Chemistry, University of Belgrade, 2011.
- (7) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.-c.; Luo, T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, 133, 14944–14947.
- (8) Yue, G.; Zhang, Y.; Fang, L.; Li, C.-c.; Luo, T.; Yang, Z. *Angew. Chem., Int. Ed.* **2014**, 53, 1837–1840.
- (9) Tsuchiya, T.; Mikami, M.; Umezawa, H.; Naganawa, H. *J. Antibiot.* **1974**, 27, 579–586. (b) Takeuchi, T.; Chimura, H.; Hamada, M.; Umezawa, H.; Yoshika, H.; Oguchi, N.; Takahashi, Y.; Matsuda, A. *J. Antibiot.* **1975**, 28, 737–742. (c) Müller, A.; Keller-Schierlein, W.; Bielicki, J.; Rak, G.; Stümpfel, J.; Zähner, H. *Helv. Chim. Acta* **1986**, 69, 1829–1832.
- (10) Mac, D. H.; Chandrasekhar, S.; Gree, R. *Eur. J. Org. Chem.* **2012**, 2012, 5881–5895.
- (11) Prasad, K. R.; Kumar, S. M. *Synlett* **2011**, 2011, 1602–1604.
- (12) Fourriere, G.; Leclerc, E.; Quirion, J.-C.; Pannecoucke, X. *J. Fluorine Chem.* **2012**, 134, 172–179.
- (13) (a) Midland, M. M.; Gallou, F. *Lithium acetylide*; *e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley and Sons, 2006. (b) Midland, M. M. *Propynylmagnesium bromide*; *e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley and Sons, 2001. (c) Paquette, L. A. *Cerium(III) chloride*; *e-EROS Encyclopedia of Reagents for Organic Synthesis*; John Wiley and Sons, 2006. (d) Anand, N. K.; Carreira, E. M. *J. Am. Chem. Soc.* **2001**, 123, 9687–9688.
- (14) (a) Marion, N.; Nolan, P. *Angew. Chem., Int. Ed.* **2007**, 46, 2750–2752. (b) Odabachian, Y.; Le Goff, X. F.; Gagosz, F. *Chem. - Eur. J.* **2009**, 15, 8966–8970. (c) Simonneau, A.; Jaroschik, F.; Lesage, D.; Karanik, M.; Guillot, R.; Malacria, M.; Tabet, J.-C.; Goddard, J.-P.; Fensterbank, L.; Gandon, V.; Gimbert, Y. *Chem. Sci.* **2011**, 2, 2417–2422. (d) Cheong, P. H.-Y.; Morganello, P.; Luzung, M. R.; Houk, K. N.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, 130, 4517–4526. (e) Hashmi, A. S. K. *Acc. Chem. Res.* **2014**, 47, 864–876.