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Atom-Economical Synthesis of Functionalized Cycloalkanes via Catalytic Redox Cycloisomerization of Propargyl Alcohols

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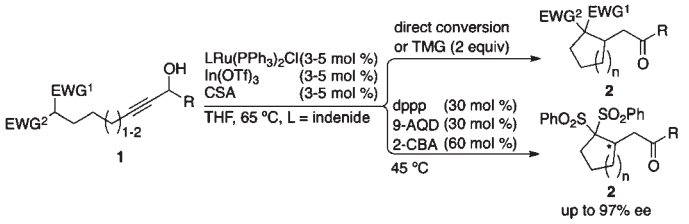
ABSTRACT



An atom-economical procedure for the direct synthesis of cycloalkanes from propargyl alcohols is reported. This high-yielding one-pot process involves a sequence consisting of a Ru-catalyzed redox isomerization of ynols into enones or an enal followed by an intramolecular Michael addition of a variety of carbon nucleophiles. Furthermore, an asymmetric variant of this protocol realized by the aid of a chiral nonracemic diamine catalyst, which provides the cyclization products in up to 97% ee, is presented.

In light of the paramount relevance of cycloalkanes, i.e. in the realm of natural product synthesis, pharmaceuticals, and material sciences, a great body of effort has been devoted to the development of new strategies for their construction. An eminent method for the chemo- and stereoselective assembly of functionalized cycloalkanes is the intramolecular Michael reaction.[1] Conventional protocols of this type usually rely on multistep procedures in which the Michael acceptor is prepared in a separate operation prior to the conjugate addition step. In particular, the synthesis of enones and enals generally requires independent redox manipulations for the implementation of the carbon−carbon and carbon−oxygen double bond, respectively.[2,3] As an alternative, our research group has focused on the direct and nondissipative conversion of primary and secondary propargyl alcohols into α,β-unsaturated carbonyl compounds via Ru-catalyzed redox isomerization.[4] In the course of our program we demonstrated that the redox isomerization is suitable for the design of novel consecutive and domino reactions[5] such as intramolecular conjugate additions of heteroatomic nucleophiles,[6] Friedel−Crafts/conjugate additions,[7] and cyclopropanations of unactivated olefins.[8]

On the basis of our previous discoveries, we became interested in the question of whether propargyl alcohols **1**, which contain a distal C−H acidic carbon nucleophile, can be redox cycloisomerized under ruthenium cocatalysis to provide a variety of cycloalkanes **2** in a one-pot operation (Scheme 1). Such a process allows for the direct and

(1) Little, R. D.; Masjedizadeh, M. R. *Org. React.* **1995**, *47*, 315.

(2) For reductions of propargyl alcohols to *E*-configured allylic alcohols, see: (a) Grob, C. A.; Gradient, F. *Helv. Chim. Acta* **1957**, *40*, 1145. (b) Jenny, E. F.; Druey, J. *Helv. Chim. Acta* **1959**, *42*, 401. (c) Oroshnik, W.; Mebane, A. D. *J. Am. Chem. Soc.* **1954**, *76*, 5719. (d) Marvel, C. S.; Hill, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 481.

(3) For chemoselective oxidations of primary and secondary allylic alcohols to the corresponding α,β-unsaturated carbonyl compounds, see: Gritter, R. J.; Wallace, T. J. *J. Org. Chem.* **1959**, *24*, 1051.

(4) (a) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 11970. (b) Trost, B. M.; Livingston, R. C. *J. Am. Chem. Soc.* **1995**, *117*, 9586.

(5) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(6) (a) Trost, B. M.; Maulide, N.; Livingston, R. C. *J. Am. Chem. Soc.* **2008**, *130*, 16502. (b) Trost, B. M.; Gutierrez, A. C.; Livingston, R. C. *Org. Lett.* **2009**, *11*, 2539.

(7) Trost, B. M.; Breder, A. *Org. Lett.* **2011**, *13*, 398.

(8) Trost, B. M.; Breder, A.; O' Keefe, B. M.; Rao, M.; Franz, A. W. *J. Am. Chem. Soc.* **2011**, *133*, 4766.

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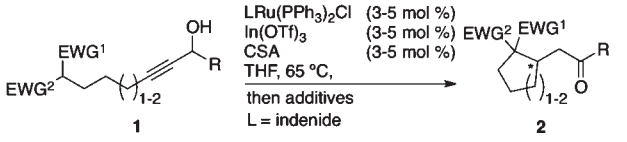
atom-economical assembly of diversely functionalized molecular frameworks from simple starting materials. In addition, this concept offers the opportunity for the design of an asymmetric process by the use of chiral cocatalysts for the conjugate addition step. It is noteworthy that the latter aspect bears significant difficulties, since the catalytic Michael addition has to be compatible with the reaction conditions necessary for the redox isomerization. Despite these challenges, we report herein an efficient protocol for the catalytic redox cycloisomerization[9,10] of propargyl alcohols and an asymmetric version thereof.

Scheme 1. Synthetic Concept



In order to verify our hypothesis, investigations began with a screening for appropriate cyclization conditions. In initial experiments propargyl alcohol **1a** was redox cycloisomerized to **2a** using IndRu(PPh_3)$_2$Cl (Ind = indenide), indium triflate, and camphorsulfonic acid (5 mol % each) in THF (0.2 M) at 65 °C followed by addition of a series of basic additives (Table 1). In the absence of any additives no cyclization product **2a** was observed at both room temperature (entry 1) and 65 °C (entry 2). Addition of cesium carbonate (100 mol %, entry 3) at 65 °C merely led to a complex mixture of multiple products. Use of 30 mol % of *N*,*N*,*N*′,*N*′-tetramethylguanidine (TMG)[11] led only to trace amounts of target structure **2a** (entry 4). However, when the amount of TMG was increased to 200 mol %, cyclohexane derivative **2a** was obtained in an excellent yield of 98% (entry 5).

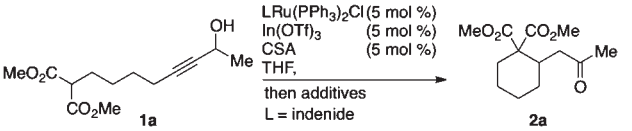
With an efficient set of conditions in hand, we continued with the exploration of the scope of the redox cycloisomerization (Scheme 2). Consequently, we synthesized a series of primary and secondary propargyl alcohols **1b**–**m** and subsequently subjected them to the new reaction protocol. In general, the method proved efficient for a variety of carbon nucleophiles such as malonates, β-ketoesters, and bis-sulfones. In the case of ynols **1a**–**h** the corresponding cyclohexane derivatives were isolated in good to excellent yields ranging from 64 to 98%. An exception was substrate **1i**, which was converted into **2i** only in a yield of 55% as a 1:1 mixture of diastereoisomers.

(9) The term "redox cycloisomerization" refers to the fact that cycloalkanes **2** are directly generated from their constitutional isomers **1** via redox isomerization and intramolecular Michael addition, irrespective of the fact that this transformation usually proceeds in two stages.

(10) For transition-metal-catalyzed cycloisomerization reactions, see: Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1.

(11) Ishikawa, T. *Superbases for Organic Synthesis: Guanidines, Amidines, Phosphazenes, and other Organocatalysts*; John Wiley & Sons Ltd: Hoboken, NJ, 2009.

Table 1. Optimization of the Redox Cycloisomerization



entry	additive	conditions	yield [%]
1	none	24 °C, 16 h	0
2	none	65 °C, 24 h	0
3	Cs_2CO_3 (100 mol %)	65 °C, 16 h	complex mixture
4	TMG[a] (30 mol %)	65 °C, 16 h	<5
5	TMG[a] (200 mol %)	65 °C, 48 h	98

[a] TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine.

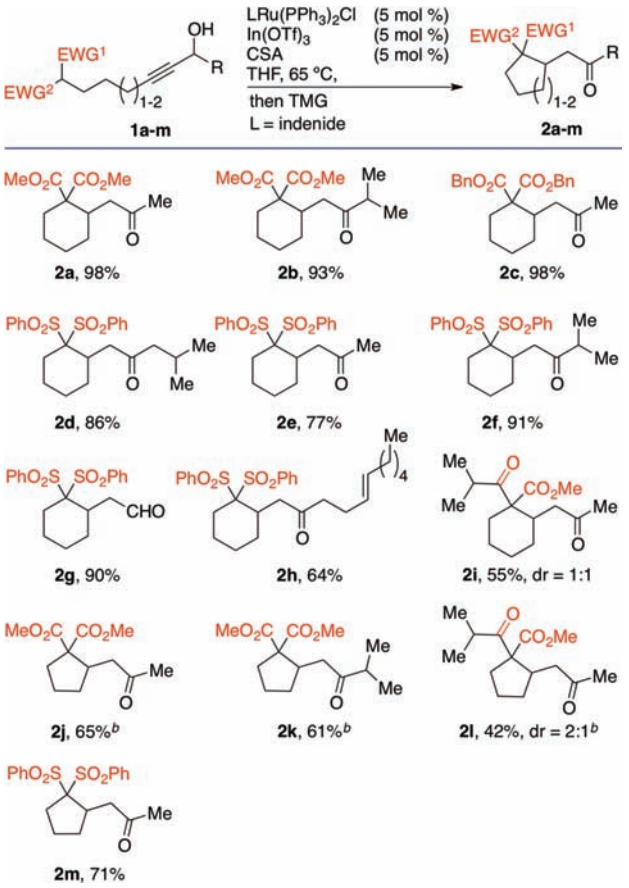
When we looked at ynols **1j**–**l** we made an interesting observation. Upon subjection of these substrates to the redox isomerization protocol, the corresponding cyclopentane derivatives **2j**–**l** were formed even in the absence of additional base in yields ranging from 42% to 65% (Scheme 2). Substrate **1m**, on the other hand, required the presence of TMG in order to convert into **2m** (71% yield). The cause for the difference in reactivity of **1j**–**l** compared to ynols containing a C_4-tether may result from the significantly faster rate of cyclization to 5-membered rings wherein deprotonation becomes the rate determining step. In the case of alcohol **1m**, however, the steric demand of the two phenylsulfone groups may hamper the direct conjugate addition, which would explain the need for an additional base. Further experiments to elucidate the mechanistic aspects of the additive-free redox cycloisomerization are currently in progress.

At this point our efforts focused on the design of an asymmetric redox cycloisomerization protocol. As previously indicated, the feasibility of a catalytic, asymmetric conjugate addition is strongly dependent on the compatibility of the respective catalyst with the reaction conditions for the redox isomerization. From previous work it was known that THF was the superior solvent for this particular step.[4] Consequently, we began to screen for appropriate catalyst systems that would allow for high levels of asymmetry during the Michael reaction in THF. For this purpose we synthesized enone **3e** (79% yield) via redox isomerization, which was subsequently used as our test substrate for the Michael reaction (Table 2). The reason why we focused on bis-sulfone nucleophiles was the fact that none of the tested bis-sulfones displayed background cyclization during the redox isomerization (cf. ynol **1m** vs **1j**–**l**). This aspect is important because in the case of C_3-tethered malonates or β-ketoesters the stereoinduction of a chiral catalyst would presumably be negatively affected by strong background reactivity.

In initial experiments, 9-amino-9-deoxyepiquinidine[12] (9-AQD) was used in combination with various Brønsted

(12) Luo, J.; Xu, L.-W.; Hay, R. A. S.; Lu, Y. *Org. Lett.* **2009**, *11*, 437.

Scheme 2. Scope of the Redox Cycloisomerization[a]



[a] Conditions: all reactions were performed in THF (0.2−0.3 M) for 16−20 h. For the intramolecular Michael reaction 1.1−2.0 equiv of TMG were used. [b] Cyclization occurred in the absence of TMG. TMG = *N*,*N*,*N*′,*N*′-tetramethylguanidine.

acid cocatalysts.[13,14] From these studies we learned that 20 mol % of the organocatalyst in combination with 40 mol % of 2-chlorobenzoic acid (2-CBA)[15] in THF at 45 °C efficiently furnished **2e** in 71% yield and 90% ee (Table 2, entry 1).[16] Unfortunately, when enone **3e** was first premixed with 5 mol % of both IndRu(PPh$_3$)$_2$Cl and In(OTf)$_3$ followed by addition of 9-AQD (20 mol %) and 2-CBA (40 mol %) no conversion was observed (entry 2). When In(OTf)$_3$ was omitted from the reaction mixture, we observed some reactivity; however, target structure **2e** was isolated only in 20% yield (entry 3). From these observations we concluded that the presence of strong Lewis acids is detrimental to the activity of the organocatalyst. Consequently, we lowered the amount of metal catalysts to

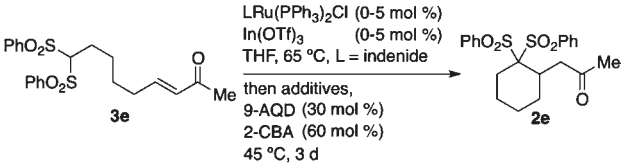
(13) Sun, X.; Yu, F.; Ye, T.; Liang, X.; Ye, J. *Chem.—Eur. J.* **2011**, *17*, 430.

(14) For a screening of Brønsted acids for the optimization of enantioselectivity, see Table 1 in the experimental section.

(15) In general, benzoic acid derivatives gave better ee's than aliphatic carboxylic acids (see Supporting Information). However, the exact reason for the superiority of 2-chlorobenzoic acid remains unclear at this point.

(16) During the investigations described in Table 2 we primarily focused on the impact of various Lewis bases on the isolated yield. Thus, we did not determine the ee values of **2e** for entries 3, 5, and 6 in Table 2.

Table 2. Optimization of the Conjugate Addition



entry	Ru-/In-cat. [mol %]	additives	yield [%]
1[a]	0/0	none	71
2	5/5	none	0
3	5/0	none	20
4	3/3	H_2O	0
5	3/3	PPh_3	35
6	3/3	dppp	65

[a] 20 mol % of 9-AQD and 40 mol % of 2-CBA were used. 9-AQD = 9-amino-9-deoxyepiquinidine; 2-CBA = 2-chlorobenzoic acid; dppp = 1,3-bis(diphenylphosphino)propane.

3 mol % in order to minimize their malign impact on the Michael reaction. Additionally, we screened for Lewis basic additives that are capable of quenching the Ru- and In-salts without negatively affecting the stereoinduction of 9-AQD.

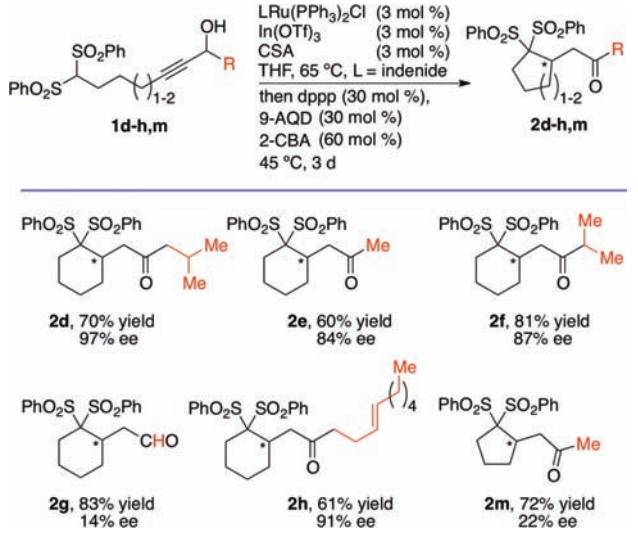
Upon addition of 5 vol % of water, based on the amount of THF, to the reaction mixture no product formation was observed (entry 4). Addition of 30 mol % of triphenylphosphine, however, led to an increased yield of 35% (entry 5). Changing to 30 mol % of bidentate 1,3-bis(diphenylphosphino)propane (dppp) afforded cyclohexane **2e** in an isolated yield of 65% (entry 6).

Application of the optimized conditions for the Michael reaction to our aspired asymmetric redox cycloisomerization proved fruitful (Scheme 3). Subjection of ynol **1e** to the new protocol afforded cyclohexane derivative **2e** in 60% yield and in 84% ee. Notably, this result demonstrates that the presence of dppp has only a marginal impact on the enantioselectivity. Even better results regarding the ee were obtained with substrates possessing a branched alkyl group in α- and *β*-position to the carbinol center (ynols **1d** and **1f**). The corresponding cyclization product **2d** was isolated in 70% yield and with an excellent ee of 97%. Homologous structure **2f** was obtained with a somewhat lower ee of 87% but in good yield (73%). Unfortunately, when primary propargyl alcohol **1g** was used, the ee decreased drastically to 14%. We speculate that the low stereoinduction is caused by a fast background reaction, which is caused by neither the ruthenium nor the indium catalyst.[17] This hypothesis is supported by the fact that conversion of **1g** to **2g** is complete within 24 h whereas the reaction time for the analogous secondary ynols is 3 d.[18] A similar observation was made for cyclopentane **2m**, which was isolated in 73% yield and 22% ee. In the cases of

(17) We did not observe any Michael addition product during the redox isomerization of ynol **1g** in the absence of base.

(18) Although all redox cycloisomerization reactions described in Scheme 3 were allowed to proceed for 3 d, TLC analysis for ynols **1g** and **1m** indicated that the reaction reached completion after 24 h.

Scheme 3. Scope of the Asymmetric Redox Cycloisomerization[a]



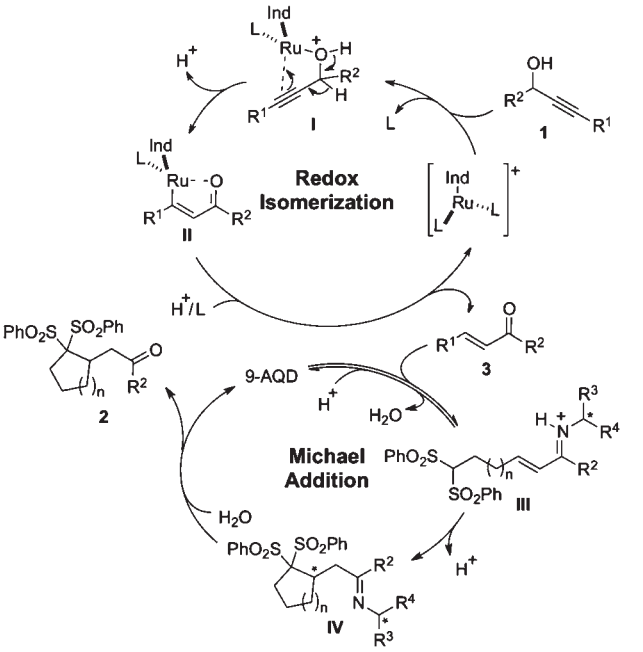
cycloalkanes **3d**−**f** and **3h** enone activation is presumably the rate limiting step (Scheme 4, iminium ion **III**).[19] For compounds **2g** and **2m**, on the other hand, deprotonation of the bis-sulfone entity is rate limiting. Consequently, the decreased enantioselectivity could be explained by the low stereocontrol exerted by the 9-amino-9-deoxyepiquinidinium counterion compared with the intramolecular control present in iminium species **III**.

Based on our previous investigations on redox isomerization reactions in combination with the present study and recent work by You et al.,[4,19] we propose the following mechanistic hypothesis for the asymmetric redox cycloisomerization (Scheme 4). In the first step, propargyl alcohol **1** is catalytically converted to α,β-unsaturated carbonyl compound **3** via 1,2-hydride migration.[4] Subsequent intramolecular Michael addition by means of 9-AQD-mediated iminium catalysis generates carbocycle **IV**, which upon hydrolysis converts into ketone **2**.

In summary, we have developed a highly atom-economical and redox neutral protocol for the direct conversion of propargyl alcohols into cycloalkanes via ruthenium and Brønsted base cocatalysis. This novel method features a broad substrate scope and generally furnishes the cyclization products in good to excellent yields. We have also demonstrated that this procedure can be easily directed in an asymmetric fashion by use of a cinchona alkaloid-derived diamine catalyst, which offers levels of enantioselectivity of up to 97% ee.

(19) Cai, Q.; Zheng, C; Zhang, J.-W.; You, S.-L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8665.

Scheme 4. Mechanistic Proposal for the Redox Cycloisomerization



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Supporting Information Available. Experimental procedures, spectrocopic data, and spectra of ^{1}H and ^{13}C NMR for the addition products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.