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Synthesis of Tetrahydropyrans from Propargyl Alcohols and 1,1-Cyclopropanediesters: A One-Pot Ring-Opening/Conia-ene Protocol

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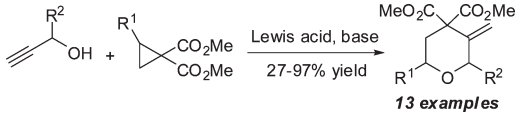
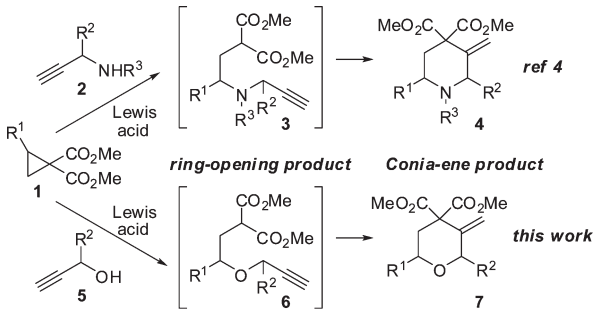


Lewis acid catalyzed ring opening of 1,1-cyclopropanediesters by the hydroxyl group of a propargyl alcohol sets up a subsequent Conia-ene cyclization to afford substituted tetrahydropyrans in a one-pot, high-yielding procedure.

The tetrahydropyran ring is an omnipresent heterocycle in the chemistry of the natural world owing largely to its presence in the pyranose sugars. In addition, the tetrahydropyran ring is a key structural feature of an enormous array of non-carbohydrate natural products. With the natural abundance of this heterocycle, it is not surprising that the synthetic chemists' repertoire contains numerous methods for its synthesis.[1]

Annulation reactions of donor−acceptor cyclopropanes[2] have received considerable attention in recent years due to their abiltity to allow rapid access to a variety of heterocycles.[3] Our group has had a long-standing interest in this field and has recently disclosed a tandem ring-opening/Conia-ene sequence involving propargyl amines and cyclopropanediesters allowing access to highly substituted piperidines.[4] Herein we

SCHEME 1. Synthesis of Piperidines and Tetrahydropyrans



wish to present an extension of this research to a convenient one-pot synthesis of tetrahydropyrans from propargyl alcohols and 1,1-cyclopropanediesters (Scheme 1).

With 1,1-cyclopropanediester **1a** and propargyl alcohol **5a** as our exploratory substrates, we set out to find a Lewis acid capable of promoting both the nucleophilic ring-opening[5] of the cyclopropane and subsequent Conia-ene[6−13] cyclization. While a variety of Lewis acids were screened (Table 1), only $In(OTf)_3$ was found to perform both functions in an adequate manner. During the screening process, it was noted that the presence of a base significantly improved the Conia-ene cyclization (perhaps as a proton shuttle); however, because of base deactivation of the Lewis acid toward the cyclopropane ring opening, it was important to use half the molar quantity with respect to the $In(OTf)_3$.

During our studies, it became apparent that soluble amine bases were most effective. Moreover, it seemed that weaker

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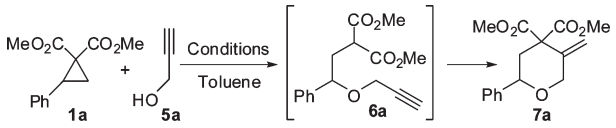
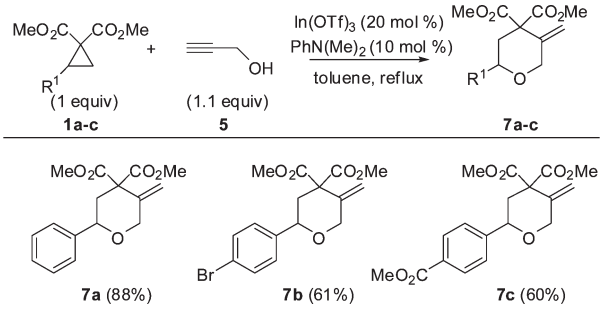
TABLE 1. Optimization of Tandem Ring-Opening/Conia-ene Cyclization



entry	base (equiv)	catalyst (equiv)	temp	yield[a]
1	none	$Zn(OTf)_2$ (0.1)	reflux	57%
2	none	$Zn(NTf_2)_2$ (0.1)	reflux	mixture[c]
3	none	$Sc(OTf)_3$ (0.1)	rt	**6a**[b]
4	none	$ZnBr_2$ (0.1)	reflux	no rxn
5	none	$In(OTf)_3$ (0.1)	reflux	28%
6	NEt_3 (1.0)	$In(OTf)_3$ (0.2) then $ZnBr_2$ (3.0)	rt to reflux	97%
7	NEt_3 (0.1)	$In(OTf)_3$ (0.2)	reflux	57%
8	DIPEA (0.1)	$In(OTf)_3$ (0.2)	rt to reflux	69%
9	K_2CO_3 (0.1)	$In(OTf)_3$ (0.2)	rt to reflux	decomp
10	pyridine (0.1)	$In(OTf)_3$ (0.2)	rt to reflux	82%
11	PPh_3 (0.1)	$In(OTf)_3$ (0.2)	rt to reflux	58%
12	2,6-lutidine (0.1)	$In(OTf)_3$ (0.2)	rt to reflux	77%
13	$PhN(Me)_2$ (0.1)	$In(OTf)_3$ (0.2)	rt to reflux	86%
14	$PhN(Me)_2$ (0.1)	$In(OTf)_3$ (0.2)	reflux	88%
15	$PhN(Me)_2$ (0.08)	$In(OTf)_3$ (0.15)	reflux	82%
16	$PhN(Me)_2$ (0.05)	$In(OTf)_3$ (0.1)	reflux	76%
17	$PhN(Me)_2$ (0.03)	$In(OTf)_3$ (0.05)	reflux	75%
18	$PhN(Me)_2$ (0.02)	$In(OTf)_3$ (0.1)	reflux	mixture[c]
19	$PhN(Me)_2$ (0.1)	$In(OTf)_3$ (0.1)	reflux	69%

[a]Isolated yield of **7a**. [b]Acyclic compound **6a** was isolated in 88% yield. [c]Product was formed as part of an inseparable mixture.

TABLE 2. Reaction Scope for $In(OTf)_3$-Catalyzed Reaction



bases, such as *N*,*N*-dimethylaniline, were superior, perhaps due to the lessened ability to deactivate the Lewis acid catalyst. Decreasing the Lewis acid catalyst loading below 20 mol % resulted in diminished yields (entries 15−17). Using very small quantities of base was also found to be detrimental to the reaction course (entry 18). With presumed optimal conditions in hand (entry 14), we set forth to survey the substrate scope and demonstrate the utility of this process.

It became apparent early on that the "optimized" conditions were somewhat limited in substrate scope. Only phenyl-substituted cyclopropanediesters bearing either no phenyl substituent or an electron-withdrawing substituent behaved acceptably under these conditions (Table 2). In the case of the electron-rich aromatic substituents, the reaction led solely to the decomposition of the acyclic intermediate **6a** (vide infra) via detrimental interaction with $In(OTf)_3$ under the refluxing conditions necessary to promote the Conia-ene process.

While disappointed at the limited scope of the reaction as it stood, we decided to reinvestigate the reaction scope of a two-step one-pot protocol (see Table 1, entry 6). These new conditions, while straying from the idea of a single catalyst, are general and technically simple. In addition, although superstoichiometric in $ZnBr_2$, this metal salt is quite inexpensive. Because the initial ring opening was allowed to proceed at room temperature, little $In(OTf)_3$-promoted decomposition was observed even for very electron-rich phenylcyclopropanes. In the case of cyclopropanes bearing an electron-withdrawing aryl substituent, ring opening was often sluggish. This was overcome by simply increasing the relative amounts of $In(OTf)_3$ and propargyl alcohol. The scope of the two-step one-pot protocol is shown in Table 3.

In almost all cases, the yields range from good to excellent. The cyclopropanediester bearing no substituent vicinal to the geminal diester moiety performed rather poorly, giving only a 27% yield of product. The reaction is not restricted to cyclopropanes with phenyl substituents. Cyclopropanes with methyl, vinyl, naphthyl, and heteroaryl substituents all performed well under these reaction conditions. It should be noted that the presence of a furan moiety on the cyclopropane was not tolerated as it underwent decomposition under the reaction conditions. Compounds **7a** and **7f** were prepared in near enantiomerically pure form (as analyzed by chiral HPLC) beginning with a cyclopropane of similar enantiomeric purity.[14] The reaction proceeded with a presumed[15] clean inversion at the cyclopropane stereogenic center.

A plausible mechanism for the two-metal one-pot procedure is shown in Scheme 2, where initial coordination of the diesters by $In(OTf)_3$ allows nucleophilic ring-opening to occur and formation of acyclic ether **6a**. Addition of NEt_3 and $ZnBr_2$ then allows for sequestering of the $In(OTf)_3$ and coordination of the diesters by zinc. Subsequent coordination of the alkyne then facilitates malonate addition to the alkyne and formation of metalate **8**. Protonation of metalate **8** then leads to the desired tetrahydropyran **7**.

(14) (*R*)-Dimethyl 2-phenylcyclopropane-1,1-dicarboxylate 98% ee, (*R*)-dimethyl 2-(4-chlorophenyl)cyclopropane-1,1-dicarboxylate 98% ee.

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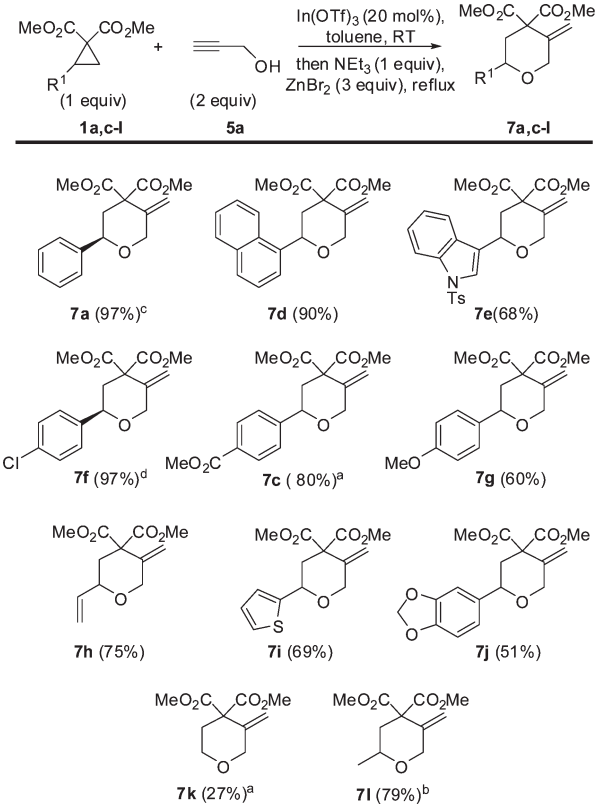
TABLE 3. Reaction Scope for $In(OTf)_3/ZnBr_2$-Catalyzed Method



[a]Propargyl alcohol (6 equiv) and $In(OTf)_3$ (0.5 equiv) were employed. [b]Propargyl alcohol (3 equiv) and $In(OTf)_3$ (0.2 equiv) were employed. [c]Product obtained in 98% ee. [d]Product obtained in 97% ee.

The effect of α-chirality on the propargyl alcohol was also investigated by treating racemic 1,1-cyclopropanediester **1a** with racemic propargyl alcohol **5b** (Scheme 3). Not surprisingly, we obtained tetrahydropyran **7m** as an equimolar mixture of *cis* and *trans* isomers. We suspect that, based on our previous observations,[4] through judicious choice of homochiral starting materials, either diastereomer of the product tetrahydropyran could be prepared as a single enantiomer.

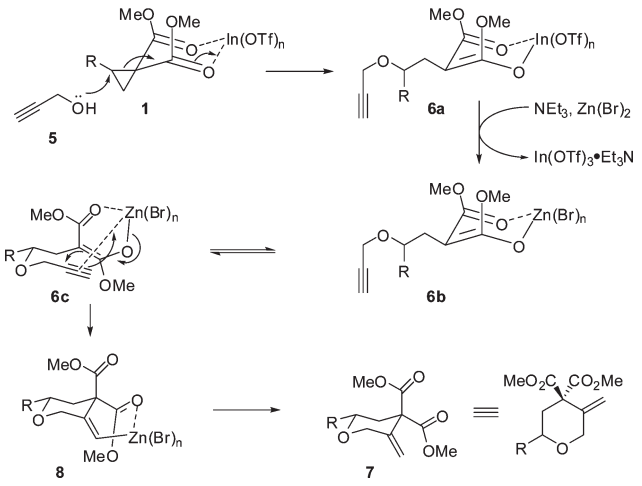
In summary, we have reported a technically simple and general synthesis of tetrahydropyrans from propargyl alcohols and 1,1-cyclopropanediesters. A single catalyst system is useful for some cases, while a two-metal/one-pot protocol is more general and may be used to prepare a wide variety of tetrahydropyrans. The application of this methodology toward the total synthesis of tetrahydropyran-containing natural products is currently underway.

Experimental Section

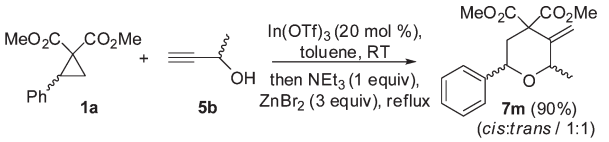
Tetrahydropyran **7a** was prepared by both methods.

$In(OTf)_3$-Catalyzed Method:. To a solution of 100 mg of cyclopropane **1a** (0.427 mmol) in 3 mL of benzene were added propargyl alcohol (24 mg, 0.427 mmol), $In(OTf)_3$ (48 mg, 0.0834 mmol), and *N*,*N*-dimethylaniline (53 mg, 0.0427 mmol). The solution was then heated to reflux, and the reaction was monitored by TLC. Upon completion, the reaction was diluted with EtOAc and then preabsorbed onto silica and purified by flash column chromatography with 10% EtOAc in hexanes. Tetrahydropyran **7a** (109 mg, 88% yield) was obtained as a pale yellow oil.

SCHEME 2. Plausible Mechanism for $In(OTf)_3/ZnBr_2$-Catalyzed Method



SCHEME 3. Effects of α-Chirality on the Propargyl Alcohol



$In(OTf)_3/ZnBr_2$-Catalyzed Method:. To a solution of 100 mg of cyclopropane **1a** (0.427 mmol) in 1 mL of benzene were added propargyl alcohol (36 mg, 0.640 mmol) and $In(OTf)_3$ (24 mg, 0.0427 mmol). The reaction was monitored by TLC. Upon complete consumption of the cyclopropane, the reaction mixture was diluted to a final volume of 3 mL of benzene, and $ZnBr_2$ (288 mg, 1.28 mmol) and NEt_3 (44 mg, 0.427 mmol) were then added. The solution was then heated to reflux and monitored by TLC. Once the reaction was completed, the solution was diluted with water and EtOAc. The aqueous layer was then extracted twice with EtOAc, and the combined organic fractions were washed once with 5% HCl and once with brine. The solvent was then removed under reduced pressure, and the resulting crude residue was preabsorbed onto silica and purified by flash column chromatography with 10% EtOAc in hexanes. Tetrahydropyran **7a** (121 mg, 97% yield) was obtained as a pale yellow oil: $R_f = 0.39$ (15% EtOAc in hexanes); ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.37−7.32 (m, 4H), 7.30−7.26 (m, 1H), 5.27 (s, 1H), 4.94 (s, 1H), 4.45−4.40 (m, 2H), 4.33 (AB dd, 1H, J = 8.4 Hz, 0.8 Hz), 3.87 (s, 3H), 3.80 (s, 3H), 2.61 (dd, 1H, J = 9.0 Hz, 1.4 Hz), 2.41 (dd, 1H, J = 9.0 Hz, 8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 170.2, 169.6, 140.9, 139.5, 128.4, 127.8, 125.9, 114.1, 76.3, 71.7, 60.6, 53.2, 52.8, 40.4; IR (thin film) ν (cm^{-1}) = 3091, 3065, 3032, 3005, 2956, 2851, 1735, 1654, 1497, 1456, 1437, 1369, 1337, 1261, 1241, 1214, 1114, 1085, 1071, 1030, 996, 920, 767, 700; HRMS (70 ev) calcd for $C_{16}H_{18}O_5$ = 290.1154, found = 290.1145.

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Supporting Information Available: Complete experimental procedures as well as ^{1}H NMR and ^{13}C NMR, IR, MS, data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.