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Convergent Evolution of Diastereomeric Mixtures of 5-Methoxypentylzirconocenes toward Trans-1,2-substituted Cyclopentanes

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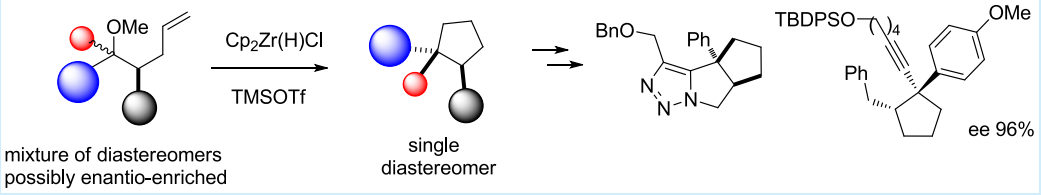

ABSTRACT: The access to 1,2- and 1,1,2-substituted trans cyclopentanes via a sequential hydrozirconation/TMSOTf-mediated cyclization applied to 5-methoxypent-1-enes is presented. Involving a transient carbocation, the reaction was shown to be diastereoconvergent. Possibly performed in a nonracemic version, the reaction proved compatible with a range of functional groups affording a large panel of cyclopentanes.

Common to a plethora of biologically active molecules,[1] the cyclopentane skeleton constitutes a privileged scaffold for the design of chiral ligands for catalysis as well as a locking element to build conformationnally constrained mimics. In this context, strategies which allow the stereocontrolled construction of carbocyclic structures including 1,2-disubstituted cyclopentanes remain of considerable interest.

A number of synthetic tools enable efficient ring closure to the five-membered carbocyclic motif, such as metathesis,[2] transition-metal-mediated intramolecular transformations including ene-reaction,[3] alkyl-Heck,[4] allylation,[5] cascade hydro-[6] and carbometalation[7]/cyclizations, and palladium-mediated [3 + 2] cycloaddition.[8] However, to achieve stereoselectivity, most of these strategies require configurational control of all the stereogenic centers prior to cyclization or via a subsequent stereoselective transformations of the intracyclic C=C double bond.

Additionally, Lewis acid mediated[9] or organo-catalyzed ring closure implying prochiral enolic systems have been reported as direct stereoselective routes to polysubstituted cyclopentanes.[10] Cascade Michael addition/cyclization[11] also constitutes an attractive and stereoselective approach for accessing polysubstituted cyclopentanes. Alternatively, radical ring-closure processes involving prochiral systems[12] might also be used to reach five-membered carbocycles.

In contrast, strategies relying on the connection of two Csp^3 through a nucleophilic substitution remain rare. Hard reaction conditions,[13] including strong bases, are often required to promote the cyclization, limiting the method to substrates bearing inert substituents. To prevent the use of strong bases for generating the C–M bond, hydrometalation constitutes an efficient and regioselective variation, particularly in the case of terminal alkenes. Among them, the hydrozirconation exhibits a high tolerance toward a large range of functional groups.[14] Although the resulting zirconocenes suffer from a lack of reactivity, it may be compensated by generating a more reactive nucleophilic species through transmetalation.[15]

Since the pioneering work of Hansawa and Taguchi related to the formation of cyclopropylmethanols from vinylepoxides under hydrozirconation conditions,[16] a complementary approach, based on the Lewis acid mediated activation of the electrophilic site, was developed to promote the ring closure. First, Hansawa and Taguchi showed that homoallylic epoxides underwent a similar and stereospecific ring closure affording cyclopentanols (Figure 1).[17] In this case, an epoxide activation is required due to the absence of a proximal Zr–O interaction. Second, Szymoniak described the access to *trans* cyclopropanes through a sequential hydrozirconation/$BF_3{\cdot}OEt_2$-assisted contraction.[18] The stereoselectivity was reported to result from a diastereoselective hydrozirconation, the consequence of a directed approach of the zirconium hydride mediated by Zr–O interaction, followed by a stereospecific ring-closure step. The mechanism was studied in-depth using marked compounds by Casey, and a W-shaped transition state evolving with an S_N2 like selectivity was proposed.[19] Additionally an access to cyclopropylboronic esters via a similar sequence hydroboration/hydrozirconation applied to propargylic silylethers was reported by Talbot.[20] Recently, we described the

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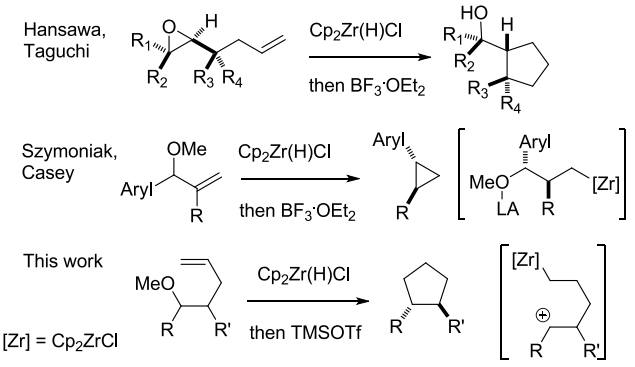


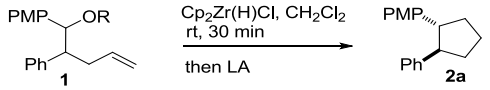
Figure 1. Context of the study.

synthesis of disubstituted alkenes from a diastereoisomeric mixture of homoallylic ethers following a similar sequence. The exclusive E selectivity was assumed to result from a cationic intermediate.[21] Therefore, if a transient carbocation could be generated, a convergent access to cyclopentanes may be envisioned from a mixture of diastereomers, thus avoiding a fastidious diastereoselective synthesis of the precursor.

In this letter, we disclose the diastereoselective preparation of *trans* di- and trisubstituted cyclopentanes from 5-methoxy alkenes through a sequential hydrozirconation/Lewis acid mediated deoxygenative cyclization.

Preliminary studies were devoted to identifying optimal conditions to promote the cyclization from model substrates susceptible to favor the delivery of a carbocation (Table 1).

Table 1. Lewis Acid Screening[a]



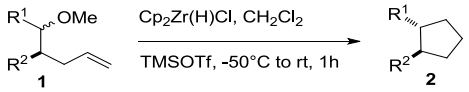
entry	1, R	LA	2a, yield (%)[b]	dr[c]
1	**1a**, CH_3	$BF_3{\cdot}OEt_2$	50[d]	ND
2	**1a**, CH_3	$AlCl_3$	77	>98:2
3	**1a**, CH_3	$TiCl_4$	80	>98:2
4	**1a**, CH_3	TMSOTf	88	>98:2
5	**1b**, TMS	$BF_3{\cdot}OEt_2$	40[d]	77:23
6	**1b**, TMS	$AlCl_3$	20	ND

[a]Reaction conditions: **3** (1 mmol), $Cp_2Zr(H)Cl$ (1.2 mmol), CH_2Cl_2 (3 mL), rt, 20−30 min, then Lewis acid (1 mmol), −50 °C for 30 min, then 30 min rt. [b]Isolated yield. [c]Calculated from the crude reaction by ^1H NMR spectrometry. [d]Conversion

Thus, **1a,b** reacted with Schwartz's reagent (1.2 equiv) in CH_2Cl_2. While the hydrozirconation proceeded well with **1a**, providing a limpid yellow solution within 30−40 min, a turbid solution was observed with **1b**. Subsequently, a Lewis acid was added to promote the cyclization. As anticipated from the latter experimental observations, lower conversions were obtained in the case of **1b**. Regarding Lewis acids, the use of BF_3 allowed the cyclization to occur, however in low yield along with degradation. In contrast, good conversions were obtained using $TiCl_4$ and $AlCl_3$. Finally, the best conditions were obtained using TMSOTf with **1a** as the starting material. Interestingly, the cyclopentane was obtained with almost complete diastereoselectivity.

To estimate the scope of the reaction, a series of diversely substituted substrates was prepared next (for details, see Supporting Information) and tested in the optimized conditions. While structural flexibility is tolerated in the *β*-position of the methoxy group (R^2), the choice of the proximal substituent (R^1) might be guided by its propensity to activate the departure of the methoxy group under Lewis acid conditions. Indeed, alkyl (Table 2, entry 5) and a deactivating

Table 2. Synthesis of Cyclopentanes 2[a]



entry	R^1	R^2	1, dr	2 yield[b] (%), dr[c]
1	PMP	PMP	**1c**, 88:12	**2c** (44), >95:5
2	4-*i*Bu-C_6H_4	4-MeO-C_6H_4	**1d**, 94:6	**2d** (53), >95:5
3	4-Cl-C_6H_4	4-Cl-C_6H_4	**1e**, 90:10	NR
4	Ph	CH_2Ph	**1f**, >95:5	**2f** (52), >95:5
5	CH_2Ph	Ph	**1g**, 75:25	NR
6	Ph	$CH_2OTBDPS$	**1h**, 100:0	**2h** (64), >95:5
7	Ph	$CH_2OTBDPS$	**1h**, 0:100	**2h** (50), >95:5
8[d]	2-thiophenyl	Ph	**1i**, 93:7	**2i** (90), >95:5
9	2-thiophenyl	$CH_2OTBDPS$	**1j**, 56:44	**2j** (39), 83:17
10	Ph−CH=CH	$CH_2OTBDPS$	**1k**, 52:48	**2k** (62), 85:15

[a]Reaction conditions: **3** (1 mmol), $Cp_2Zr(H)Cl$ (1.3 mmol), CH_2Cl_2 (3 mL), rt, 20−30 min, then TMSOTf (1 mmol), −50 °C for 30 min, then 30 min rt. [b]Isolated yield [c]Determined from ^1H NMR of the crude reaction, [d]TMSOTf was added at 0 °C.

phenyl group (entry 3) are not suitable for promoting the cyclization. In contrast, aryl (entries 1, 3−4, and 6−7), 2-thiophenyl (entries 8 and 9), and a styryl group (entry 10) are sufficiently activating to ensure the formation of the corresponding cyclopentanes. Except for **2j** and **2k**, good *trans*-selectivity was observed with most substrates, even starting from mixtures of diastereomers.

Nucleophilic substitution of activated alcohols[22] promoted by a Lewis or Brønsted acid is established to follow an S_N1 pattern.[23] Eventually, the nucleophilic attack of the transient carbocation may be stereoinduced by a chiral structural element. Thus, a high level of diastereocontrol could be reached in intramolecular reactions.[24] Possibly, the diastereoselectivity may decline from a thermodynamic equilibration when the cyclization step is reversible.[24d] In contrast, cyclization involving the S_N2 process from activated alcohols is rare and requires a transient chiral intimate ion pair,[25] or a simultaneous activation of both the leaving group and the nucleophile.[26]

In the present case, the formation of *trans* cyclopentanes **2**[27] would plausibly originate from a carbocation, generated via TMSOTf-mediated activation, which irreversibly evolves in a selective manner (Figure 2). This was supported by applying identical reaction conditions to each diastereomeric form of **1h**, which both led to *trans* **2h** (Table 2, entries 6 and 7).[28]

Structural diversity remains a major objective in synthetic methodology development. In this context, it would be appealing to extend the present strategy to more versatile substrates. From that perspective, the introduction of a C≡C triple bond as the additional substituent was envisioned. This would (i) meet the electronic criteria for generating a cationic intermediate, which should even be facilitated; (ii) possibly secure a diastereoselective ring-closure step since the disparity in size between the two lateral chains would be retained; and (iii) offer multiple possibilities of further functionalization. However, the access to the corresponding cyclopentane relies

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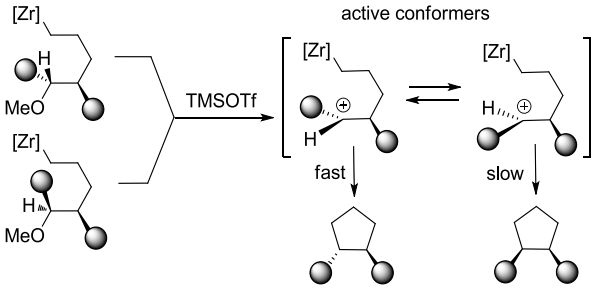


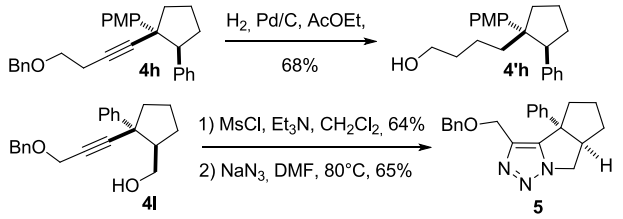
Figure 2. Rationale of evolution of the diastereomeric zirconocenes.

on the chemoselective hydrozirconation of the C=C double bond, which remains possible owing to the higher substitution degree of the C≡C triple bond.

A series of substrates **3** were prepared and submitted to the same cyclization conditions. Pleasantly, cyclopentanes **4**[29] incorporating diverse combinations of substituents (Table 3, entries 1−4 and 7−12) were obtained in good yield, except in the particular case of **3f** (R^1 = Bn, entry 6), where a competitive evolution toward the enyne seemed to prevail.[30] Interestingly, a high level of diastereocontrol was observed in most cases (dr 93:7 to >95:5), except for **4d**, presumably due to low discrimination between the *n*-butyl and the alkynyl chain. Noteworthy, a large panel of alkynyl fragment (R^3 = Ph, $SiMe_3$ or hydroxyl-protected chains) is compatible with a selective hydrozirconation. In comparison with the previous series, the incorporation of an alkynyl chain seems to compensate the presence of an alkyl chain (entry 4) or a deactivating aryl fragment (entry 3), enlarging the structural diversity achievable. However, it remains necessary to incorporate a conjugated alkynyl fragment to generate the carbocation (entry 4 vs 5), and the reaction time must be increased to 1 h.

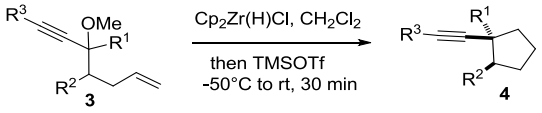
The synthetic interest of the method was illustrated by first accessing cyclopentane **4′h** bearing both an alkyl and an aryl substituent at the same position through Pd-catalyzed hydrogenation. Second, tricyclic compound **5** was prepared via intramolecular alkyne−azide cycloaddition (Scheme 1).

Scheme 1. Synthetic Applications



Finally, the possibility to synthesize cyclopentanes in a nonracemic version was evaluated. Since the reaction was proven to involve a transient carbocation, the strategy for preparing the cyclopentane precursor was devoted toward solely controlling the configuration of the irremovable stereogenic center at the homoallylic position. We opted for a diastereoselective acylation of Evans-type substrates[31] followed by a reduction, which did not need to be diastereoselective, to afford the desired diol.[32] Thus, **6**[33] was deprotonated using LDA, and benzoyl chloride or *p*-methoxybenzoyl chloride was added to give respectively ceto-carbamates **7l** and **7m** respectively, isolated as single stereoisomers. Subsequent global reduction using $LiBH_4$[34] followed by silylation of the primary alcohol and methylation of the secondary completed the enantio-enriched synthesis of **1l** and **1m** (Scheme 2). For the preparation of **3m**, a similar approach was employed. The deprotonation/benzylation sequence[35] applied to **6**[36] provided **8** as a single diastereomer. Subsequent conversion into the Weinreb amide **9**, followed by successive additions of 4-methoxyphenyllithium and [6-(*tert*-butyldiphenylsilyloxy) hex-1-ynyl]lithium afforded the tertiary alcohol which was ultimately methylated to afford **3m** (Scheme 2). Substrates **1l,m** and **3m** were submitted to the previously described cyclization conditions to give enantioenriched cyclopentanes with nearly complete conservation of the enantiomeric integrity. Products **2l**,[37] **2m**, obtained in their free alcohol form, and **4m** were obtained with ee values greater than 90% (Scheme 2).

Table 3. Synthesis of Cyclopentanes 4[a]



entry	3	R^1	R^2	R^3	4 yield (%),[b] dr[c]
1	**3b**	1-Naphtyl	$(CH_2)_2OBn$	Ph	**4a** (51), 93:7
2	**3c**	4-MeO-C_6H_4	$(CH_2)_3OBn$	$(CH_2)_2OBn$	**4b** (70), 92:8
3[d]	**3d**	4-F-C_6H_4	$(CH_2)_3OBn$	4-Me-C_6H_4	**4c** (66), 96:4
4[d]	**3e**	*n*-Bu	$(CH_2)_3OBn$	Ph	**4d** (74), 79:21
5[d]	**3f**	CH_2Ph	Ph	$(CH_2)_2OBn$	–
6	**3g**	CH_2Ph	Ph	Ph	ND
7	**3h**	4-MeO-C_6H_4	Ph	$SiMe_3$	**4g** (84), 94:6
8	**3i**	4-MeO-C_6H_4	Ph	$(CH_2)_2OBn$	**4h** (76), >95:5
9	**3j**	2-thiophenyl	Ph	$SiMe_3$	**4i** (90), >95:5
10	**3k**	4-MeO-C_6H_4	Ph	2-thiophenyl	**4j** (58), 90:10
11	**3l**	2-thiophenyl	Ph	CH_2OBn	**4k** (65), >95:5
12	**3m**	4-MeO-C_6H_4	$CH_2OTBDMS$	CH_2OBn	**4l**[e] (80), >95:5

[a]Reaction conditions: **3** (1 mmol), $Cp_2Zr(H)Cl$ (1.3 mmol), CH_2Cl_2 (3 mL), rt, 20−30 min, then TMSOTf (1 mmol), −50 °C for 30 min, then 30 min rt. [b]Isolated yield. [c]Determined from ^1H NMR of the crude reaction mixture. [d]1 h at −50 °C, 1 h, then, 30 min rt. [e]Free alcohol was obtained.

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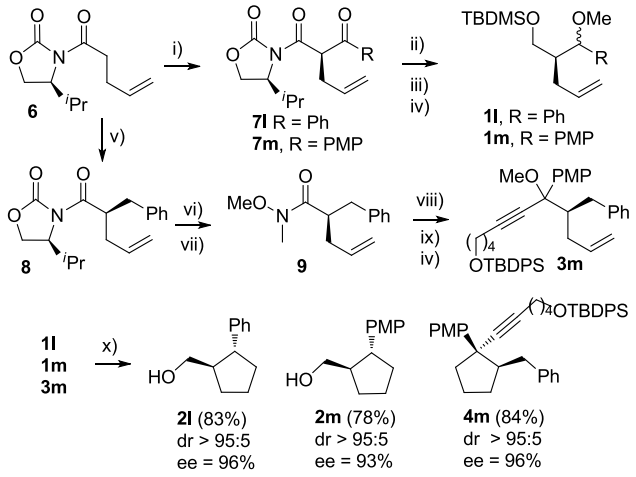
Scheme 2. Synthesis of Enantio-enriched Cyclopentanes[a]



[a]Reagents: (i) LDA, THF, then acylchloride; (ii) $LiBH_4$, MeOH; (iii)TBDMSCl, imidazole, CH_2Cl_2; (iv) NaH, THF, then MeI; (v) LDA, THF, then BnBr; (vi) LiOOH, THF/H_2O; (vii) EDCI, MeONHMe·HCl; (viii) *p*-MeO-C_6H_4Li, THF; (ix) TBDPSO–$(CH_2)_4$–C≡CLi, THF; (x) $Cp_2Zr(H)Cl$, CH_2Cl_2, then TMSOTf.

In summary, a diastereoselective access to 1,2- and 1,1,2-substituted cyclopentanes based on a sequential hydrozirconation/TMSOTf-mediated cyclization is reported. Involving the generation of a transient carbocation which evolves selectively in favor of the *trans* isomer, this method was proven to be flexible since it may be launched from both diastereomeric forms of the starting material. Possibly performed in a nonracemic version, this approach may be of synthetic interest for the synthesis of functionalized cyclopentane-based scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03998.

Experimental procedures, characterization, and copies of ^1H and ^{13}C NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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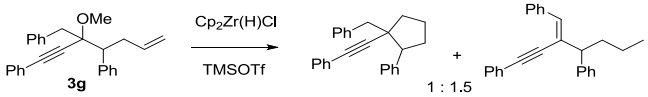

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