# Stereoselective Synthesis of Tri- and Tetrasubstituted Olefins by Tandem Cyclization Addition Reactions Featuring Vinyl Radicals**

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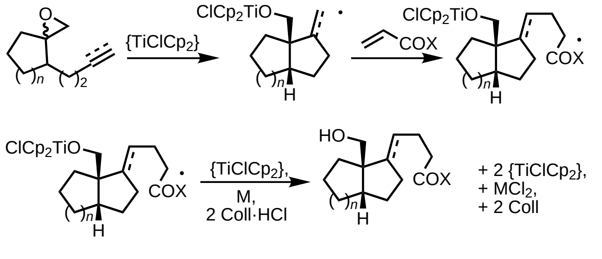
Harald Bluhm

Reactions leading to structurally complex molecules by transformation of simple precursors with high mass transfer under catalytic conditions are attractive for synthesis.[1] A promising candidate in this respect is the combination of our titanocene-catalyzed cyclization[2] of suitably unsaturated epoxides with intermolecular additions to $\alpha,\beta$-unsaturated carbonyl compounds (Scheme 1).[3] The resulting transformation is an example of a tandem radical sequence with a cyclization addition.[4] An especially attractive feature of this reaction is the possibility of generating vinyl radicals as intermediates for the intermolecular synthesis of olefins. To the best of our knowledge this latter transformation has only rarely been realized stereoselectively, especially in the case of tetrasubstituted alkenes. We are only aware of the use of tributylstannyl- and phenylselenyl-substituted vinyl radicals in this context.[5]



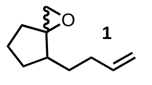
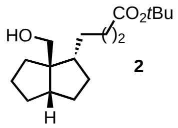
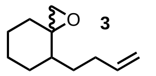
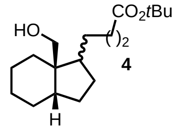
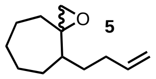
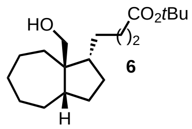
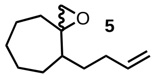
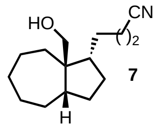
M = Zn or Mn, Coll = 2,4,6-Me$_3$-pyridine

Scheme 1. General concept for the titanocene-catalyzed tandem reactions involving vinyl radicals.

We started our investigation with olefins as radical acceptors in cyclizations. Some of our results are summarized in Table 1. The epoxides were synthesized according to reference [2e].

The tandem reaction yielded the desired products in reasonable to high yields. Noticeable amounts of undesired product resulting from intermolecular addition without cyclization (13 %) were only formed with **3** as substrate (Table 1, entry 2). In terms of kinetics, this is remarkable since the intermolecular additions of simple radicals to $\alpha,\beta$-unsaturated carbonyl compounds should compete substantially with simple 5-*exo* cyclization reactions.[3,7] The absence of this type of product in the reaction of **5** with acrylonitrile, the most reactive radical trap employed, is especially noteworthy (Table 1, entry 4). We suggest that the $\beta$-titanoxy radicals are conformationally predisposed for cyclization and that the inductive effect of the $CH_2OTiCp_2Cl$ group retards additions to the electron-deficient $\alpha,\beta$-unsaturated carbonyl compounds. The diastereoselectivities of the two-step process are in the same range as for simple cyclizations.[2e]

Table 1. Titanocene-catalyzed tandem reactions with alkenes in THF.[a]

| Entry | Substrate | Product | Yield [%] |
|---|---|---|---|
| 1 |  **1** |  **2** | 51,[b] d.r. > 97:3 |
| 2 |  **3** |  **4** | 51,[c] d.r. = 55:45 |
| 3 |  **5** |  **6** | 68,[d] d.r. = 55:40:5 |
| 4 |  **5** |  **7** | 78,[e] d.r. = 56:39:5 |

[a] For the synthesis and experimental details, see [6] and the Supporting Information. [b] **1**: d.r. > 98:2, 5 mol % cat., 9 equiv of acrylate. [c] **3**: d.r. = 90:10, 10 mol % cat., 5 equiv of acrylate. [d] **5**: d.r. = 56:44, 10 mol % cat., 9 equiv of acrylate, minor isomer: *cis* orientation of $CH_2OH$ and alkyl chain. [e] **5**: d.r. = 56:44, 10 mol % cat., 9 equiv of acrylnitrile, minor isomer: *cis* orientation of $CH_2OH$ and alkyl chain.

The chemoselectivity of the tandem reaction is expected to be even lower in the case of alkynes as radical acceptors, because their cyclizations are about one order of magnitude slower than those of the corresponding alkenes.[8] Our results with these substrates are summarized in Table 2. The epoxides were synthesized according to reference [2e].

Epoxide **8** gave the desired product **9** in good yield and with high diastereoselectivity (diastereomeric ratio d.r. > 97:3; Table 2, entry 1). Basically no products (< 3 %) resulting from intermolecular addition without cyclization or from simple cyclization were observed. Remarkably, preorganization and electron deficiency of the $\beta$-titanoxy radicals allow for a successful tandem reaction even in the case of the slower cyclization.

A key characteristic of this reaction is the necessity to use a solvent with a lower hydrogen donor propensity than THF, which reduces highly reactive vinyl and aryl radicals by hydrogen atom abstraction to yield the products of simple cyclization.[9] The general ease of reduction has probably precluded the use of vinyl radicals for intermolecular additions in typical chain reactions in the presence of stannanes or silanes.

In addition to displaying a low hydrogen donor ability, the substitute for THF must also enable a fast reduction of

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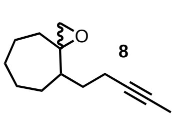
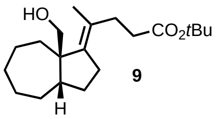
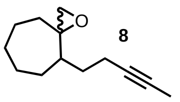
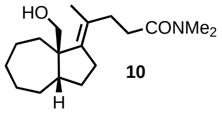
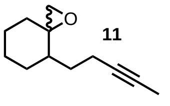
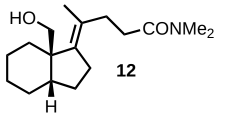
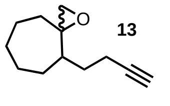
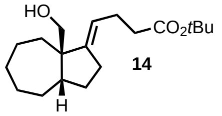
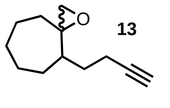
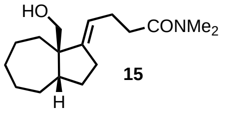
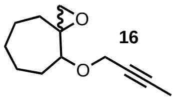
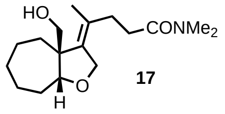
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

Table 2. Titanocene-catalyzed tandem reactions with alkynes in ethyl acetate.[a]

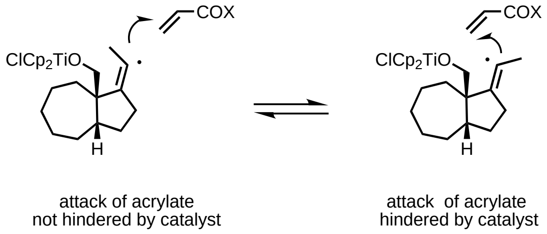
| Entry | Substrate | Product | Yield [%] |
|---|---|---|---|
| 1 |  **8** |  **9** | 69,[b] d.r. > 97:3 |
| 2 |  **8** |  **10** | 67,[c] d.r. = 92:8 |
| 3 |  **11** |  **12** | 54,[d] d.r. = 95:5 |
| 4 |  **13** |  **14** | 58,[e] d.r. > 97:3 |
| 5 |  **13** |  **15** | 55,[f] d.r. > 97:3 |
| 6 |  **16** |  **17** | 68,[g] d.r. = 96:4 |

[a] d.r. refers to the $E$:$Z$ ratio of the olefins. For the assignment of the configuration by NOE measurements, see the Supporting Information. [b] **8**: d.r. = 97:3, 20 mol% cat., 9 equiv of acrylate. [c] **8**: d.r. = 97:3, 20 mol% cat., 9 equiv of amide. [d] **11**: d.r. = 97:3, 20 mol% cat., 1.5 equiv of acrylate. [e] **13**: d.r. = 97:3, 10 mol% cat., 9 equiv of acrylate. [f] **13**: d.r. = 97:3, 20 mol% cat., 9 equiv of amide. [g] **16**: d.r. = 86:14, 20 mol% cat., 9 equiv of amide.

[$Cp_2TiCl_2$] by Zn in order to maintain the catalytic cycle. In this process the titanium reagents and $ZnCl_2$ must be solvated. We found that benzene, diethyl ether, and *tert*-butyl acetate did not fulfill the requirement of fast reduction. Of the polar solvents investigated—those which dissolved the salts and reduced titanium(IV)—EtOAc gave the best yields and lowest amounts of side products formed upon simple cyclization. Acetonitrile, acetone, *N*-methylpyrrolidone (NMP), and $\gamma$-butyrolactone gave distinctly inferior results.

Therefore, our modified reaction allows the formation of vinyl radicals under conditions that enable intermolecular C–C bond formation. The results observed so far suggest that vinyl radicals are well suited for the highly stereoselective synthesis of unfunctionalized tri- and tetrasubstituted olefins. Tetrasubstituted olefins are often difficult to prepare stereoselectively by other methods. A rationale for the origin of the selectivity in the reaction of the rapidly inverting vinyl radicals is presented in Scheme 2.

It is of interest to note that the reduction of the same vinyl radicals proceeds with varying selectivities (between 65:35 and 77:23). Therefore, the steric interactions of the catalyst and the acrylates as radical traps are essential for high stereoselectivity.



Scheme 2. Possible explanation for the origin of diastereoselectivity in vinyl radical additions.

Only during the synthesis of trisubstituted olefins were we able to detect minor amounts (3–10%) of the cyclization product. In these cases the more reactive disubstituted vinyl radical is formed. Our reaction is not confined to acrylates as radical traps; acrylamides are also useful. Tetrahydrofurans, for example, **17**, can be efficiently synthesized. The formation of **12** proceeds smoothly in reasonable yield. Compounds of this type may serve as models for the C and D rings of modified steroids with a double bond that can be further functionalized. They should thus be of general interest for the synthesis of important biologically active compounds.

In summary, we have devised a radical tandem reaction based on titanocene-catalyzed epoxide opening. This reaction features the use of vinyl radicals in the highly stereoselective intermolecular synthesis of tri- and tetrasubstituted olefins.

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[1] a) B. M. Trost, *Science* **1991**, *254*, 1471; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259.

[2] a) A. Gansäuer, M. Pierobon, H. Bluhm, *Angew. Chem.* **1998**, *110*, 107; *Angew. Chem. Int. Ed.* **1998**, *37*, 101; b) A. Gansäuer, H. Bluhm, M. Pierobon, *J. Am. Chem. Soc.* **1998**, *120*, 12849; c) A. Gansäuer, T. Lauterbach, H. Bluhm, M. Noltemeyer, *Angew. Chem.* **1999**, *111*, 3112; *Angew. Chem. Int. Ed.* **1999**, *38*, 2909; d) A. Gansäuer, H. Bluhm, *Chem. Rev.* **2000**, *100*, 2771; e) A. Gansäuer, M. Pierobon, H. Bluhm, *Synthesis* **2001**, 2500.

[3] Comprehensive review of the factors influencing selectivity: H. Fischer, L. Radom, *Angew. Chem.* **2001**, *113*, 1380; *Angew. Chem. Int. Ed.* **2001**, *40*, 1340.

[4] This concept is used relatively rarely. For examples and a review, see a) G. Stork, P. M. Sher, *J. Am. Chem. Soc.* **1987**, *108*, 303; b) G. Stork, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 149; c) M. Journet, M. Malacria, *J. Org. Chem.* **1992**, *57*, 3085; d) J. C. Lopez, A. M. Gomez, B. Fraser-Reid, *J. Chem. Soc. Chem. Commun.* **1993**, 762; e) R. N. Saicic, Z. Cekovic, *Tetrahedron Lett.* **1994**, *35*, 7845.

[5] Vinyl radicals have been used in cyclization reactions and in atom transfer reactions: a) G. Stork, R. Mook, Jr., *J. Am. Chem. Soc.* **1983**, *105*, 3720; b) M. R. Elliot, A.-L. Dhimane, M. Malacria, *J. Am. Chem. Soc.* **1997**, *119*, 3427; c) L. Fensterbank, E. Mainetti, P. Devin, M. Malacria, *Synlett* **2000**, 1342; d) A. Martinez-Grau, D. P. Curran, *J. Org. Chem.* **1995**, *60*, 8332; e) D. L. J. Clive, M. Cantin, *J. Chem. Soc. Chem. Commun.* **1995**, 319; f) D. L. J. Clive, W. Yang, *Chem. Commun.* **1996**, 1605; g) A. Martinez-Grau, D. P. Curran, *Tetrahedron* **1997**, *53*, 5679. For an example of a bimolecular generation of vinyl radicals, see h) J. O. Metzger, F. Bangert, *Chem. Ber.* **1994**, *127*, 673. For the use of tributylstannyl- and phenylselenyl-substituted vinyl radicals in intermolecular additions, see i) A. Ogawa, I. Ogawa, N. Sonoda, *J. Org. Chem.* **2000**, *65*, 7682; j) K. Miura, H. Saito, D. Itoh, T. Matsuda, N. Fujisawa, D. Wang, A. Hosomi, *J. Org. Chem.* **2001**, *66*, 3348; k) K. Miura, H. Saito, N. Fujisawa, D. Wang, H. Nishikori, A. Hosomi, *Org. Lett.* **2001**, *3*, 4055.

[6] Typical experimental procedure: Preparation of **7**: Collidine hydrochloride (394 mg, 2.50 mmol), zinc (131 mg, 2.00 mmol), [$TiCl_2Cp_2$] (25 mg, 0.10 mmol), acrylonitrile (0.60 mL, 9.00 mmol), and epoxide **5**

(180 mg, 1.00 mmol) were mixed in THF (10 mL). The mixture was stirred for 65 h at room temperature and then heated at reflux for 15 h. Purification by $SiO_2$ flash chromatography (22 cm, $\varnothing$2 cm, AcOEt:cyclohexane (97:3)→(20:80), 20 mL) allowed the partial separation of three diastereoisomers of the desired product as pale yellow oils: *cis*-**7** (71 mg, 30%) and *trans*-**7** (112 mg, 48%, d.r. = 92:8). Combined yield: 78%, d.r. = 56:39:5. Starting material (25 mg, 14%) was also recovered. See the Supporting Information for spectroscopic details.

[7] a) B. Giese, G. Kretzschmar, *Chem. Ber.* **1983**, *116*, 3267; b) B. Giese, G. Kretzschmar, *Chem. Ber.* **1984**, *117*, 3160.

[8] A. L. J. Beckwith, C. H. Schiesser, *Tetrahedron* **1985**, *41*, 3925.

[9] Vinyl radicals: T. V. RajanBabu, W. A. Nugent, *J. Am. Chem. Soc.* **1994**, *116*, 986; aryl radicals: J. C. Scaiano, L. C. Stewart, *J. Am. Chem. Soc.* **1983**, *105*, 3609; S. J. Garden, D. V. Avila, A. L. J. Beckwith, V. W. Bowry, K. U. Ingold, J. Lusztyk, *J. Org. Chem.* **1996**, *61*, 805.

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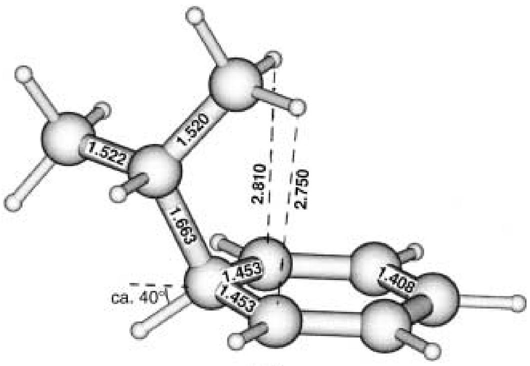
# Do Isopropyl and *tert*-Butyl Cations Form π Complexes with Benzene?**

Dietmar Heidrich*

The question of formation of π complexes in electrophilic aromatic substitution (EAS) has been debated for a long time.[1–4] The answer to this question is fundamental for setting up the mechanism of EAS and, therefore, for the interpretation of the kinetic data. Quantum chemistry plays a key role in the assessment of the complex formations. Herein we deal with the identification of π complexes that may be formed from benzene and carbocations.

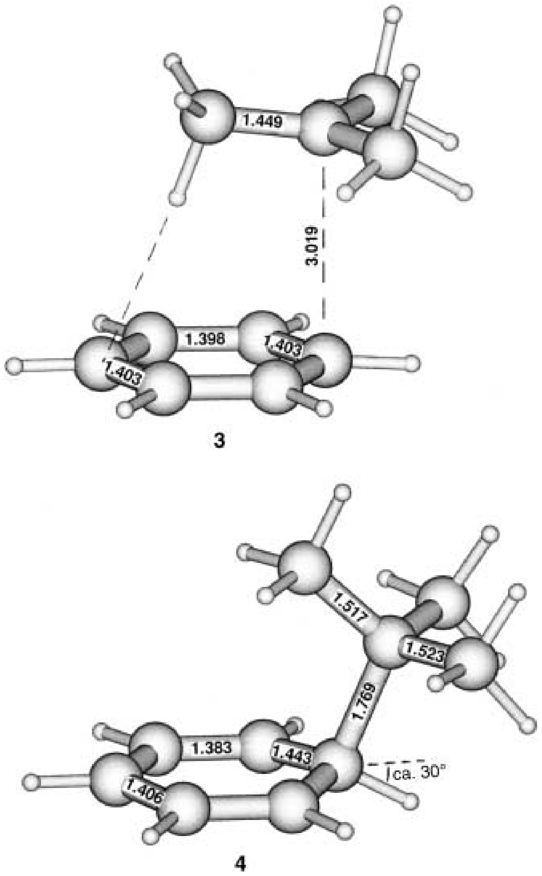
If we initially consider the structure of protonated benzene, π complexes of benzene with $H^+$ are not found by using the potential energy surface of the benzene–$H^+$ system. The only minimum is formed by the σ complex (benzenium ion).[5,6] The latter is also observed under mass spectrometric conditions[7] as well as in superacidic acids.[8] A "face" protonation is strongly disfavored.[5,6] The question arises, whether the knowledge about the protonation is qualitatively also valid for the carbocation attack on benzene.

The attack of $CH_3^+$ on benzene leads barrierless to a σ complex.[9] Our quantum-chemical studies on the interaction of the isopropyl cation with benzene do not give a π-complex intermediate (without the inclusion of electron correlation a conflicting result is obtained[10]). Like $CH_3^+$, the naked isopropyl cation approaches the benzene molecule barrierless to form the σ complex **1a** (Figure 1). In a recent theoretical paper on the alkylation of naphthalene,[11] π-complex formation was not included. We do find a π complex (**3**) for the attack of the *tert*-butyl cation ($t$Bu$^+$) on benzene preceding the σ complex **4** (Figure 2). In contrast to the results in reference [10], the cationic electrophile is not centered above the ring centroid. The "face" structure **5a** ($C_3$) is, analogously to benzene–$H^+$, a saddle point of index 2 and is $\Delta H^\circ(0) = 2.5$ kcal mol$^{-1}$ higher in energy than the σ complex (≈ 7 kcal mol$^{-1}$ with respect to $\Delta E_{\text{pot}}$, Table 1). Another three quasi-"face" structures **5b** ($C_s$) are saddle points of index 1. They are $\Delta H^\circ(0) = 2.1$ kcal mol$^{-1}$ more unstable than the σ complex (6 kcal mol$^{-1}$ with respect to $\Delta E_{\text{pot}}$). The most probable position of the $t$Bu$^+$ (definded by the position of the central C($\delta^+$)atom, $C_{t\text{Bu}^+}$) is calculated to be along the ring carbon atoms and their C–C bonds. Directly over the ring carbon atoms (distance $C_{t\text{Bu}^+}$–$C_{\text{benzene}} = 3.02$ Å) there is a



**1a**

Figure 1. The σ complex **1a** of the isopropyl cation with benzene ($C_1$ symmetry).



**3**

**4**

Figure 2. The π complex **3** ($C_s$) and the σ complex **4** ($C_s$) of the system [benzene + *tert*-butyl cation] (numbering according to Table 1; bond lengths [Å], angles [°]).

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