Catalysis

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Synthesis of Dihydropyrrolizine and Tetrahydroindolizine Scaffolds from Pyrroles by Titanocene(III) Catalysis

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Abstract: *A synthetic approach to dihydropyrrolizine and tetrahydroindolizine scaffolds from pyrroles has been developed. The key step, a titanocene(III)-catalyzed radical arylation that proceeds by C–H functionalization is atom-economical and tolerates a large variety of functional groups. The reaction is therefore attractive for the swift assembly of functional and structural diversity.*

Pyrrole and its derivatives are important compounds since many natural products containing the pyrrole core display interesting biological activity. Prime examples are the lamellarin natural products which show a wide range of biological activity against multiple cancer cell lines, HIV targets, and multidrug resistance reversal.[1] As a consequence, synthetic pyrroles have attracted considerable attention in pharmaceutical research.[2] The drug Atorvastatin, used for the treatment of high cholesterol blood levels, highlights the power of combining pyrrole with different pharmacophores. The development of Atorvastatin emphasizes a shortcoming of classical pyrrole synthesis.[3] The de novo construction of the pyrrole heterocycle was necessary for the introduction of each variation of the substitution pattern.[4]

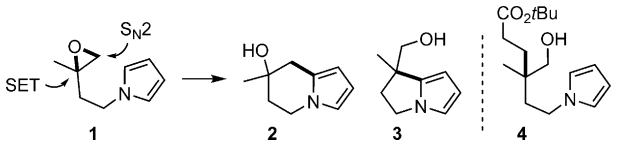
A complementary approach is the functionalization of the intact pyrrole core.[5] It provides an efficient and highly flexible approach for the generation of chemical diversity in a minimum amount of operational steps. To be broadly applicable, such reactions must tolerate functional groups, proceed under mild reaction conditions, and under complete atom economy. These goals are most readily realized with catalytic addition reactions featuring either C–H activation or C–H functionalization.[6]

Herein we report a titanocene-catalyzed radical arylation with pyrroles featuring epoxides as radical precursors. Radical generation from epoxides through reductive electron transfer (ET) from titanocene(III) reagents proceeds with high chemoselectivity and tolerates a large variety of functional groups.[7] Radical addition to the pyrrole results in C–C bond formation. The rearomatization occurs by an ET from the radical σ-complex to the pending titanocene, the critical step of the sequence, and proton transfer.[8] Because of the typically mild reaction conditions during these steps, it can be expected that our approach will circumvent the problems associated with classical acid or Lewis acid mediated Friedel–Crafts alkylations with pyrroles.[9]

The epoxide **1** (Table 1) is an especially appealing substrate for the evaluation of our concept. Tanis and Raggon have shown that a ZnI_2-mediated (2 equiv in C_6H_6) S_N2 reaction of **1** yields the tetrahydroindolizine derivative **2** (74%).[10] Our titanocene(III)-catalyzed reactions proceed by ET and leads to the dihydropyrrolizine **3** in 86% yield. The reaction is in line with radical generation at the more-substituted carbon atom of the epoxide. To rule out the unlikely generation of a tertiary cation, the radical was trapped with *t*-butyl acrylate to give **4** at room temperature and at 66 °C. In agreement with a study on the radical arylation with anilines,[8b,d] and comparison with slow cyclizations,[8f,g] the results suggest an upper limit for the rate constant of radical addition of 10^3 at 298 K. Therefore, radical addition to pyrroles is relatively slow. The high yields of **3** highlight the fact that the alkyl radicals generated under our reaction conditions are fairly persistent. Moreover, neither Coll*HCl, nor $MnCl_2$, nor Coll*HCl and Mn initiated the arylation reaction.

$[Cp_2Ti^{III}OTf]$ is a recently introduced catalyst[8e] which opens epoxides more slowly than $[Cp_2TiCl]$, and thus leads to faster rearomatization after radical addition to arenes. Since the use of $[Cp_2Ti^{III}OTf]$ results in a lower yield of **3**, rearomatization is not critical in our radical arylation with pyrroles and therefore epoxide opening is the slow step.

Table 1: Effect of the reaction conditions on the reaction pathway between nucleophilic substitution and radical ring opening/addition.



Entry	Reaction conditions	Conv. [%]	Product	Yield [%]
1	2 equiv ZnI_2[a]	100	**2**	74[f]
2	5 mol% $[Cp_2Ti^{III}Cl]$[b]	100	**3**	86
3	20 mol% $MnCl_2$[c]	0	–	–
4	20 mol% Coll*HCl[c]	17	–[d]	–
5	20 mol% Mn/Coll*HCl[c]	< 5	–[d]	–
6	5 mol% $[Cp_2Ti^{III}OTf]$[c]	81	**3**	66
7	5 mol% $[Cp_2Ti^{III}Cl]$, Acrylate[e]	100	**4**	70

[a] PhH, RT, 1 h. [b] 5 mol% $[Cp_2TiCl_2]$, 20 mol% Mn, 20 mol% Coll*HCl, THF, reflux, 3 h. [c] THF, reflux, 3 h. [d] Chlorohydrin formation. [e] 5 mol% Cp_2TiCl_2, 2 equiv Mn, 2.5 equiv Coll*HCl, 5 equiv *tert*-butyl acrylate, THF, reflux, 3 h, or RT, 18 h. [f] Literature; see Ref. [10]. Coll = 2,4,6-collidine, Cp = C_5H_5.

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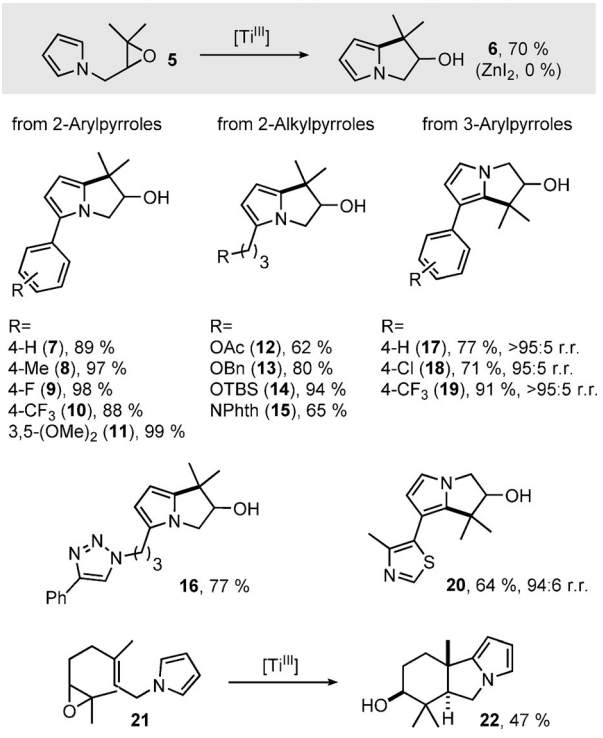
Based on these encouraging results, we explored the substrate scope of the formation of dihydropyrrolizines (Table 2). Dihydropyrrolizines are present in analgesic drugs (Ketorolac, Licofelone) and are metabolites of pyrrolizine alkaloids in animals.[11] While substrate **5** underwent product formation to form **6**, the ZnI_2-mediated cyclization did not show any conversion. 2-Aryl-substituted pyrroles are very good substrates for our reaction and led to high yields of the isolated dihydropyrrolizines **7**–**11**. Phenyl groups with electron-withdrawing as well as electron-donating substituents and pharmaceutically important fluorine-containing functional groups are readily tolerated. Moreover, our reaction conditions are compatible with hydroxy protecting groups, such as OAc, OBn, OTBS (**12**–**14**), and the phthalimide moiety (NPhth; **15**). The same holds true for heterocyclic motifs, such as triazole (**16**) and thiazole (**20**). These elements are commonly employed to generate structural and functional diversity and are important pharmacophores.[12] Therefore, our reaction should be of interest for applications in the synthesis of biologically active pyrrolizines and indolizines.

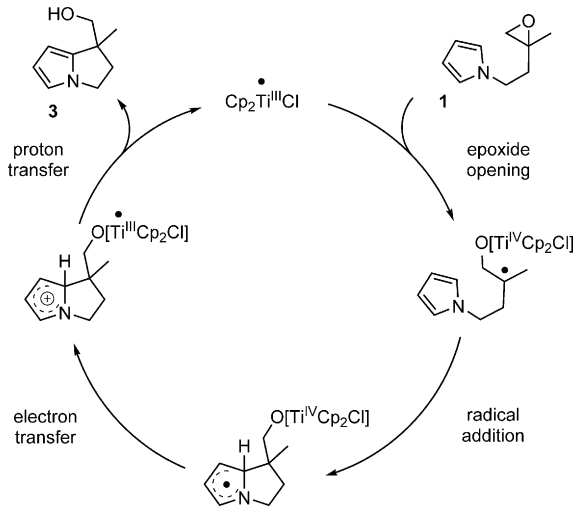
Table 2: Substrate scope of dihydropyrrolizine formation.



Reaction conditions: 5 mol% $[Cp_2TiCl_2]$, 20 mol% Mn, 20 mol% Coll*HCl, THF, reflux, 3 h. TBS = *tert*-butyldimethylsilyl.

The mechanism of the arylation is shown in Scheme 1. It features reductive epoxide opening, radical addition to the pyrrole, ET to yield the cationic σ-complex, and rearomatization by proton transfer.

A useful aspect of the reaction of 3-aryl-substituted pyrroles is that the regioselectivity of radical addition is in agreement with related studies.[13] We found that the reaction



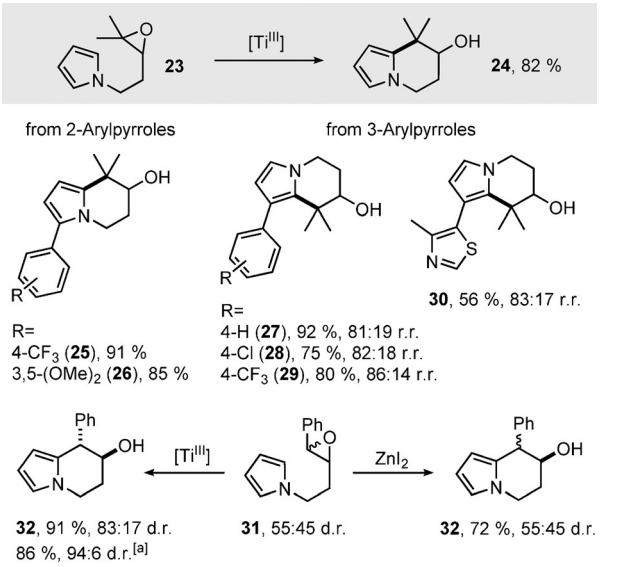
Scheme 1. Proposed mechanism for the radical arylation of pyrroles in the synthesis of **3** in analogy to the radical arylation with anilines.[8]

takes place at the sterically less accessible carbon atom with excellent regioselectivity (> 94 : < 6 r.r.) and is independent of the electronic nature of the aryl substituent (**17**–**20**; Table 2). The structural assignment is based on the ^{1}H NMR coupling constants in analogy to related compounds.[14] Thus, the stabilization of the forming radical center by the aryl group is more relevant than repulsive steric interactions between the tertiary radical and the arene.

Finally, we examined whether radical addition to a pyrrole can also be carried out in cascade reactions. The reaction of **21** yields the desired steroidal product **22** in 47 % yield as a single isomer (Table 2). The process features a 6-*endo* cyclization followed by the pivotal radical addition to the arene. It is the first example of this type of transformation and can be regarded as a proof-of-principle for a novel type of radical epoxy polyene cyclization.[15] It should be highly attractive for the synthesis of pyrrole-containing steroid derivatives.

Another class of important pyrrole derivatives are tetrahydroindolizines—common motifs in alkaloids that show diverse biological activity and have attracted considerable attention because of their Taxol™-like behavior, as in the case of Rhazinal.[1,16] Under our reaction conditions the model substrate **23** (Table 3) was readily converted into the tetrahydroindolizine **24**. With 2-aryl substituted substrates, the desired products **25** and **26** were obtained in very good yields. The CF_3 substituent and the two OMe groups, as models for electron-withdrawing and -donating substituents, respectively, demonstrate that the results are similar to those of the corresponding dihydropyrrolizines (Table 1). We observed an interesting trend for the functionalization of 3-arylpyrrole substrates. Compared to dihydropyrrolizine synthesis somewhat diminished regioselectivities for radical addition were observed for **27**–**30** (Table 3). Tetrahydroindolizines are less strained than the corresponding dihydropyrrolizines. Therefore, the transition states for radical addition should be earlier for tetrahydroindolizines. The radical stabilization of the forming benzylic radical will therefore be less relevant. Consequently, the regioselectivity in the formation of **27**–**30** is lower than for **17**–**20**.

Table 3: Substrate scope of tetrahydroindolizine formation.



Reaction conditions: 5 mol% $[Cp_2TiCl_2]$, 20 mol% Mn, 20 mol% Coll*HCl, THF, reflux, 3 h or 2 equiv ZnI_2, PhH, RT, 1 h.
[a] $[(t\text{BuC}_5\text{H}_4)\text{TiCl}_2]$ as catalyst.

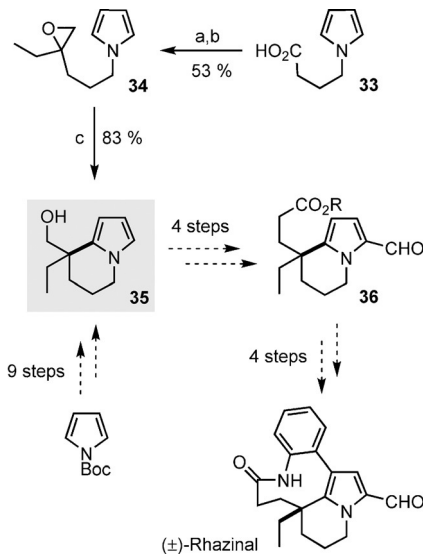


Figure 1. Step-economic optimization of the Rhazinal synthesis through titanocene(III) catalysis. a) CDMT, *N*-methylmorpholine (NMM), MeONMeH*HCl, then EtMgBr; b) Me_3SOI, NaH; c) 2.5 mol% $[Cp_2TiCl_2]$, 10 mol% Mn, 10 mol% Coll*HCl, 10 mmol scale. CDMT = 2-chloro-4,6-dimethoxy-1,3,5-triazine.

An intriguing aspect of our reaction is the control of diastereoselectivity for the addition of secondary radicals. In principle catalyst control can be exerted in this step, thus resulting in a diastereoconvergent process. We demonstrated this point in the transformation of **31** (Table 3). From the 55:45 mixture of the substrate the product **32** was obtained as a 94:6 mixture of *trans* and *cis* isomers with the bulky $[(t\text{BuC}_5\text{H}_4)_2\text{TiCl}_2]$ as a precatalyst. $[Cp_2TiCl_2]$ resulted in an inferior result, whereas the ZnI_2-mediated S_N2 reaction leads, as expected, to the same ratio of diastereoisomers in substrate and product. Therefore, besides a higher yield and lower catalyst loading the radical arylation is also superior to the S_N2 reaction because of its diastereoconvergent character.

So far, we have used our radical arylation with pyrroles for the generation of structurally and functionally diverse dihydropyrrolizines and tetrahydroindolizines. However, our method is also of interest for applications in natural products synthesis. This application is highlighted by the preparation of **35**, an intermediate in the synthesis of Rhazinal[17] (Figure 1), on gram scale (10 mmol) from **34** with a 2.5 mol% catalyst loading in 83% yield. Thus, the scale up of our reaction can be carried out with a reduction of catalyst loading. The other reported synthesis of **35** requires nine steps from a Boc-protected pyrrole. From **35**, Banwell's intermediate **36** and eventually Rhazinal were prepared in four and eight additional steps, respectively.[18]

In summary, we have developed a titanocene(III)-catalyzed[19] radical arylation with pyrroles for the synthesis of dihydropyrrolizines and tetrahydroindolizines. The catalytic, atom-economical radical reaction[20] proceeds with low catalyst loading and by C–H functionalization. It allows the rapid generation of functional and structural diversity and is of substantial interest for the synthesis of biologically active substances and natural products.

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