Diastereoselective Ce(O*i*Pr)$_3$-Catalyzed Pinacol Couplings of Aldehydes**

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In general, 1,2-diols can be generated by bishydroxylation of olefinic double bonds[1] or reductive coupling of carbonyl compounds.[2] The latter method plays an important part in the synthesis of HIV-protease inhibitors[3] and natural products such as taxol.[4] The reaction has to be performed in a diastereoselective fashion to synthesize these compounds. Economic and ecological reasons have meant that transition metal catalyzed pinacol couplings are of current interest. The catalytic cycles known so far allow the use of the catalytic low-valent metal species down to 1 mol%.[5] The formation of the active coupling reagent takes place by in situ reduction using metals such as manganese, magnesium, or zinc. Fürstner[6] was the first to develop a catalytic reaction by using trimethylsilyl chloride to cleave the metal–oxygen bond in the intermediate formed. The application of this methodology to pinacol couplings allowed disilylated diols to be obtained.[5, 7]

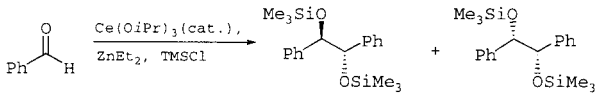
Gansäuer observed high diastereoselectivities of up to 98.5:1.5 for carbonyl reductions by using catalytic amounts of racemic ethylene-bis-(η^5-tetrahydroindenyl)titanium dichloride [(ebthiTiCl$_2$)][8] and in situ reduction with zinc.[9] A big disadvantage of this methodology is the fact that only aromatic and α,β-unsaturated aldehydes can be coupled; aliphatic aldehydes do not react under these reaction conditions.

By using low-valent samarium and vanadium species, respectively, Endo et al.[7a] and Hirao et al.[7d] demonstrated that aromatic as well as aliphatic aldehydes can be coupled in a catalytic fashion. In these cases high diastereoselectivities could only be obtained for sterically demanding substrates such as cyclohexylcarbaldehyde. The *rac*:*meso* ratio decreased to 50:50 on coupling aliphatic aldehydes.

Cerium reagents can be used widely in synthetic organic chemistry as a result of their oxophilicity.[10] Besides the diastereoselective addition of organocerium reagents to carbonyl compounds,[11] the reduction of α,β-unsaturated ketones to allylic alcohols with NaBH$_4$ in the presence of cerium trichloride[12] is of great synthetic interest. However, a catalytic application of cerium compounds has up until now remained unknown.

Herein we report on cerium(III) isopropanolate catalyzed pinacol couplings of carbonyl compounds with diethylzinc as the reductive agent. Instead of the expected addition of an ethyl group to the carbonyl function the reductive coupling of two aldehydes to 1,2-diols could be observed. To the best of our knowledge this represents the first cerium-catalyzed reaction in organic synthesis. Table 1 shows the influence of the reaction time, reaction temperature, and the amount of catalyst on the yield and diastereoselectivity for the reductive coupling of benzaldehyde. Excellent yields and high diastereoselectivities of disilylated 1,2-diols could be achieved in favor of the *rac*-isomer under noncatalytic conditions (entry 1). Diastereoselectivity and yield did not change remarkably even if only a catalytic amount of cerium reagent was employed. An increase of diastereoselectivity could be achieved by decreasing the reaction temperature, but in this case lower yields were observed (entry 4). The best reaction conditions were observed by adding benzaldehyde over several hours to the reaction mixture. In this case 1,2-bis(trimethylsiloxy)-1,2-diphenylethane could be obtained in a yield of 84% and a diastereoselectivity of 97:3 in favor of the

Table 1. Pinacol coupling of benzaldehyde (**1**) to give 1,2-bis(trimethylsiloxy)-1,2-diphenylethane (**2**) under various reaction conditions.



1 **2a** **2b**

Entry	Amount of cat. [mol%]	*t* [h]	*T* [°C]	Yield (**2**) [%]	**2a**:**2b**
1	100	15	25	90	98:2
2	10	12	25	73	96:4
3	5	12	25	70	95:5
4	5	12	−15	48	98:2
5	3	15[a]	25	84	97:3
6	0	15	25	0	–

[a] Addition of PhCHO over 10 h.

rac-diol (entry 5). A by-product of 1-phenyl-1-propanol was isolated (16%), which resulted from the addition of an ethyl group from diethylzinc to the carbonyl function over the prolonged reaction time. No reaction to the coupling product could be observed if the cerium catalyst was absent (entry 6).

In order to investigate the scope and limitations of this pinacol-type coupling reaction different aldehydes were converted into their corresponding diols under optimized reaction conditions. As shown in Table 2 substituted aromatic aldehydes could be coupled reductively in yields of 73–84% with diastereoselectivities of up to 98:2. Thereby the mesomeric effects of the substituents in the aromatic aldehydes show only a small influence on the yield and diastereoselectivity (entries 1–4).

In this context it is remarkable that even aliphatic aldehydes could undergo pinacol coupling despite their known very limited tendency to do so. The coupling of secondary and tertiary aldehydes proceeded smoothly in yields of 54–64% (entries 5–8) and diastereoselectivities of up to 98:2. The comparison of the reductive coupling of isovaleraldehyde (entry 7) and cyclohexylcarbaldehyde (entry 8) shows clearly the steric demand of the six-membered

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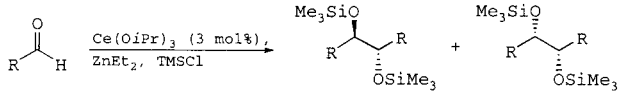
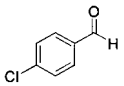
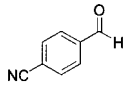
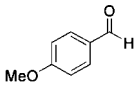
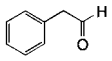
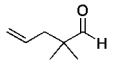
Table 2. Pinacol couplings of aromatic and aliphatic aldehydes under optimal catalytic conditions.



3 **4a** **4b**

Entry	Aldehyde	Yield (**4**) [%]	**4a**:**4b**
1		84	97:3
2		76	98:2
3		74	94:6
4		73	95:5
5		57	90:10
6		54	88:12
7		62	92:8
8		64	98:2
9		71	96:4
10		65	95:5

ring, which enforces an increase in the diastereoselectivity. Moreover, pivalaldehyde, which up until now could not be coupled reductively in a catalytic fashion, was converted into its corresponding disilylated 1,2-diol (entry 9) in a yield of 71%. In this case the presence of a double bond was also tolerated (entry 10). Nevertheless aliphatic aldehydes without any β-substitution such as hexanal cannot be coupled reductively with this catalytic system.

The pinacol coupling presented here also allows preparations on a large scale, which is of great interest for industrial applications. For example, 5.74 g (81%) of 1,2-bis(trimethylsiloxy)-1,2-diphenylethane could be isolated after conversion of 4.24 g (40 mmol) of benzaldehyde. In this procedure the amount of the applied cerium(III) isopropanolate was reduced down to 1 mol%.

The reaction mechanism of this reductive coupling is not yet clear and is therefore the subject of current investigations. The following mechanisms seem to be possible: the zinc hydride that results from disintegration of diethylzinc seems to serve as a reductive agent and reduce cerium(III) isopropanolate to cerium(II) isopropanolate, which itself reacts with the carbonyl group to give the ketyl with regeneration of Ce^{III}. On the other hand, one could imagine that the reaction mechanism is dominated by a one-electron transfer of diethylzinc[14] to the carbonyl group complexed by means of cerium(III) isopropanolate in analogy to the Grignard reaction.[13] The ethyl radical cannot be attached to the sterically demanding complexed ketyl. The pinacol then develops by recombination of two ketyls.

In summary, the advantage of the presented pinacol coupling can be characterized as follows: besides the high diastereoselective coupling of aromatic aldehydes, even aliphatic aldehydes can be coupled with high diastereoselectivities. According to this method the pinacol coupling of sugar and amino aldehydes to pharmacological interesting diols should also succeed.

Experimental Section

The reactions were carried out in an argon atmosphere using Schlenk techniques. Substances which are sensitive against moisture and air were stored in a glove box. $Ce(OiPr)_3$ was synthesized according to the procedure described in ref. [15].

General procedure: A 1M solution of diethylzinc in hexane (10 mL, 10 mmol) was added to $Ce(OiPr)_3$ (48 mg, 0.15 mmol, 3 mol%) in a Schlenk tube. Subsequently, a 1M solution of cyclohexylcarbaldeyde in THF (5.0 mL, 5.0 mmol) and a 1.5M solution of trimethylsilyl chloride in THF (5.0 mL, 7.5 mmol) were added slowly (5–15 h). After the addition of a saturated aqueous solution of ammonium chloride (20 mL), the reaction mixture was extracted with diethyl ether (50 mL, $\times 3$), the combined organic layers were dried over magnesium sulfate, and the solvent was removed by evaporation. The residue was purified by flash chromatography to yield 0.59 g (64%) of 1,2-bis(trimethylsiloxy)-1,2-dicyclohexylethane (Table 2, entry 8). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 0.12$ (s, 18H; $SiMe_3$), 1.11–1.81 (m, 20H; CH_2), 2.18–2.27 (m, 2H; CH), 3.65 (d, $J =$ 6.5 Hz, 2H; C*H*OSiMe$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta = 1.10$ ($SiMe_3$), 25.76 (C3), 26.57 (C4), 27.14 (C2), 41.96 (C1), 68.46 (*C*OSiMe$_3$).

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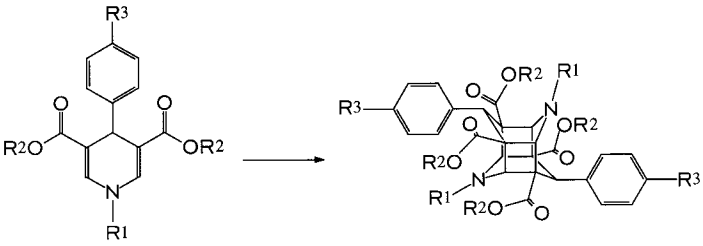
The First Functionalized 6,12-Diazatetrakishomocubanes**

Andreas Hilgeroth* and Ute Baumeister

Despite all efforts, accessibility of cage compounds analogous to cubane is limited. These compounds have presented a constant synthetic challenge since the first cubane compound was obtained.[1, 2] The limited development of novel functionalization reactions such as photochemical carboxylation[2, 3] has led to the synthesis of compounds with interesting pharmacological effects: This includes the carcinogenic effect of phenyl-substituted cubanes and substituted bishomocubanes and the recently observed anti-HIV effect of carboxylated cubanes.[2, 4] Initial efforts in combinatorial chemistry of cubanes have made accelerated discovery of new substances possible.[5] Since this only involves derivatives and not new basic structures, the challenge of finding alternative possibilities for synthesizing new cage compounds remains.

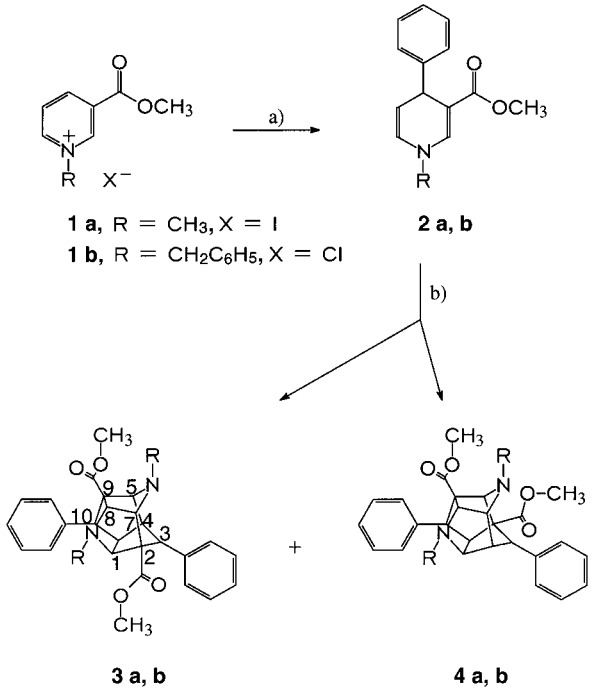
By the use of topochemically controlled photodimerization of symmetric 4-aryl-1,4-dihydropyridines to form centrosymmetric 3,9-diazatetraasteranes, we were recently able to develop a process for synthesizing tetraasteranes that are analogous to aza compounds in almost quantitative yield (Scheme 1).[6] These cubane analogons currently hold interest as novel HIV-1 protease inhibitors.[7]



Scheme 1. Formation of 3,9-diazatetraasteranes from 4-aryl-1,4-dihydropyridines.

Here, the first C_2-symmetric and asymmetric 6,12-diazatetrakishomocubanes are presented. They were obtained, totally unexpectedly, as the main products from the reaction of asymmetric 4-aryl-1,4-dihydropyridines, and enrich the pool of interesting cage compounds.

Starting from N-alkyl-substituted pyridinium compounds **1**,[8] the 4-aryl-1,4-dihydropyridines **2**[9] can be obtained in over 90% yield by regioselective reaction with equimolar amounts of phenylmagnesium chloride in the presence of catalytic amounts of copper(I) iodide[10] (Scheme 2).



Scheme 2. a) PhMgCl, CuI (cat.), THF, RT; b) *hν*, MeOH/THF.

Irradiation of solutions of 4-aryl-1,4-dihydropyridines **2** by Ultra-Vitalux lamps ($\lambda \geq 270$ nm), with excitation of the 1,4-dihydropyridine chromophores at $\lambda_{max} = 348$ nm (**2a**) or 346 nm (**2b**), resulted in the dimerization products **3** and **4** in overall yields of more than 80%. ^{1}H NMR spectroscopy showed that the C_2-symmetric compound **3** is characterized by a simple set of proton signals for the two 1,4-dihydropyridine

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