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Asymmetric Friedel−Crafts Alkylation of Pyrroles with Nitroalkenes Using a Dinuclear Zinc Catalyst

Barry M. Trost* and Christoph Müller

Department of Chemistry, Stanford University, Stanford, California 94305-5080

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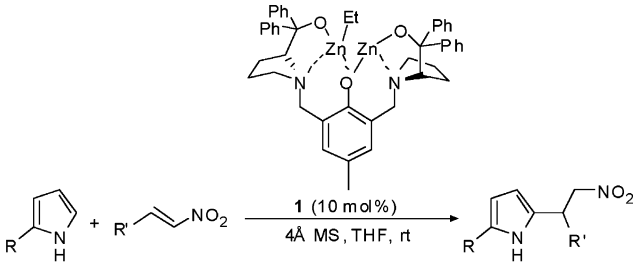
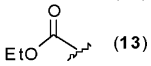
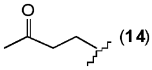
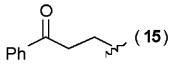
Since first reported in the year 1877,[1] the Friedel−Crafts reaction has gained substantial synthetic and industrial significance as an immensely powerful tool to effect C−C bond-formations.[2] Recently, there have been studies conducted with the aim of developing asymmetric and catalytic versions of this important transformation.[3,4] Among the stereoselective alkylations of aromatic and heteroaromatic compounds, reports about the use of pyrroles, especially unprotected pyrroles, remain rare.[5] Pyrroles are abundant in natural products,[6] medicinal agents,[7] and a number of intermediates in multistep syntheses.[8] Because of the relative instability of pyrroles toward acidic environments, classical Friedel−Crafts conditions are unsuitable for this class of compounds. Instead, mild reaction conditions are required to implement a useful Friedel−Crafts protocol for these substrates. Herein we report the use of our dinuclear zinc bis-ProPhenol complex[9] as an efficient catalyst to conduct asymmetric Friedel−Crafts alkylations of unprotected pyrroles with nitroalkenes, to prepare 2-substituted and 2,5-disubstituted pyrroles with an asymmetric carbon atom in the α-position. The nitro-compounds were chosen because of the strong electron withdrawing character and the synthetic versatility of that functional group.[10] The bis-ProPhenol complex has previously been used in a number of efficient, catalytic enantioselective transformations and has been applied successfully to a number of natural product syntheses.[11]

To optimize the reaction conditions, pyrrole was reacted with nitroalkene **2**. The dinuclear zinc complex **1** was prepared as previously reported by treating the bis-ProPhenol ligand with 2 equiv of Et_2Zn in THF at room temperature.[9] Our studies indicated that an excess of 3 equiv of pyrrole leads to the highest yields and stereoselectivities. A decrease of the catalyst loading below 10 mol %, the use of toluene as solvent or an increase of the reaction temperature resulted in lower yields and selectivities. As conditions of choice, we used THF at room temperature and a catalyst loading of 10 mol % in the presence of molecular sieves (4 Å).

To explore the scope of the reaction, various nitroalkenes were reacted with pyrrole (Table 1). First, aromatic substituents were used as R′ (entry 1−5). In all these cases, excellent enantioselectivities were obtained, which ranged from 87% for the *o*-methoxy substrate **5** to 97% for the tolyl substituted compound **2**. The position of the methoxy-substituent of compound **4** and **5** (ortho vs para) did not affect either the reactivity or selectivity of the reaction. An improvement of the yield was observed by using a furanyl substituent (entry 6). This finding cannot be rationalized by a simple coordination of the furan−oxygen atom of nitroalkene **7** to the dinuclear zinc complex, for the additional oxygen atoms in substrates **12** and **13** give lower yields and selectivities (vide infra). Compared to the furanyl-derived substrate **7**, the thiophene derived nitroalkene **8** gave a slightly increased enantioselectivity of 97% (entry 7). In addition to the aromatic and heteroaromatic substituents R′ presented above, entries 8−12 show examples for alkyl substituents R′. The best result in these cases was obtained for the cyclohexyl-substituted compound **9** (entry 8) which gave an excellent yield and selectivity. Both branched and straight chain alkyl groups on the nitroalkene as in compounds **10** and **11** (entries 9 and 10) gave very high enantioselectivities.

Table 1. Reaction of Various Pyrroles with Nitroalkenes[a]



entry	R	R'	ee[b]	yield
1	H	4-Me-Ph (**2**)	97%	58%
2	H	Ph (**3**)	94%	61%
3	H	4-MeO-Ph (**4**)	93%	56%
4	H	2-MeO-Ph (**5**)	87%	52%[c]
5	H	3-Br-Ph (**6**)	97%	49%
6	H	2-furanyl (**7**)	94%	90%
7	H	2-thiophenyl (**8**)	97%	58%
8	H	cyclohexyl (**9**)	92%	92%[c]
9	H	*i*-Pr (**10**)	90%	52%
10	H	*n*-Pr (**11**)	96%	56%
11	H	 (**12**)	76%	34%
12	H	 (**13**)	56%	38%[d]
13	 (**14**)	**7**	85%	61%
14	**14**	**10**	15%	60%
15	 (**15**)	**7**	88%	52%
16	**15**	**10**	63%	67%

[a] Reaction performed with (*S*,*S*)-complex **1** (10 mol %), pyrrole or pyrrole derivative (3 equiv), nitroalkene (1 equiv) and molecular sieves (4 Å) in THF at room temp. [b] Determined by chiral HPLC. [c] b.r.s.m. [d] Reaction performed with the (*R*,*R*)-ligand and Et_2Zn.

As mentioned above, it was hoped that by introducing further oxygen atoms into the nitroalkene, the yield could possibly be enhanced like in the case of compound **7**. Therefore, substrates **12** and **13** were prepared (entries 11 and 12). In both cases however, the additional oxygen-atoms did not increase yield or selectivity.

Next, we examined the behavior of substituted pyrroles. These substrates were prepared by direct addition reactions starting from pyrrole. In combination with our Friedel−Crafts protocol, we were able to gain access to 2,5-disubstituted pyrroles in a simple two-step sequence (eq 1). For these transformations, we used the furanyl-nitroalkene **7** and the *iso*-propyl-nitroalkene **10** as examples for an aromatic and a noncyclic, aliphatic substituent R′, respectively

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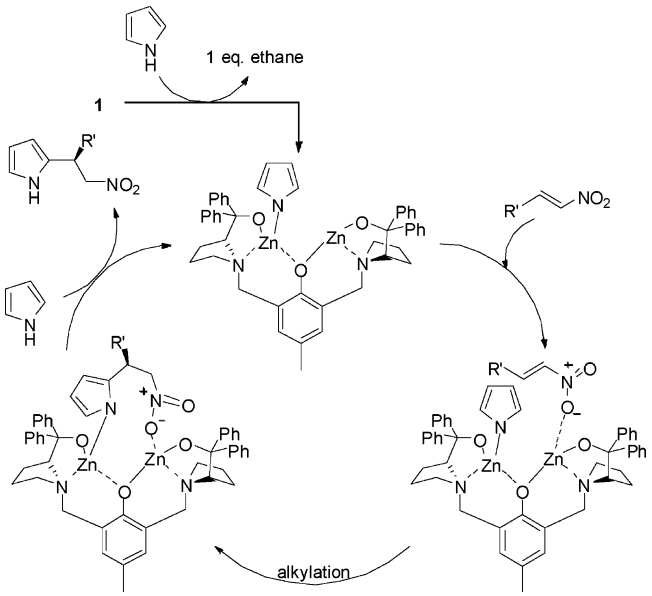
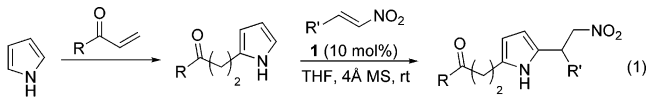
Scheme 1. Proposed Catalytic Cycle



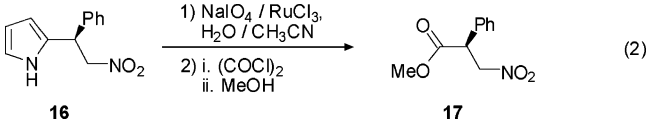
(entries 13−16). We were pleased to observe that the MVK-derived compound **14** and the phenylvinyl ketone-derived substrate **15** both showed high stereoselectivities and yields in the conversion with nitroalkene **7**. In the case of nitroalkene **10** however, only pyrrole **15** gave good yields and selectivities (entry 16).



R=Me (**14**): microwaves, 230 °C, 10 min., 55%
R=Ph (**15**): DCM, $InCl_3$, rt, 43%

To rationalize the observed results, we propose a mechanism that involves the deprotonation of pyrrole by precatalyst **1** accompanied by the formation of 1 equiv of ethane (Scheme 1). The nitroalkene coordinates to this catalyst and undergoes the alkylation reaction. The catalytic cycle is closed by a proton exchange with an incoming pyrrole to release the product and reform the active catalyst.

The absolute stereochemistry of the products was determined by comparison with a literature known compound, **17**.[12] This was accomplished by an oxidation−esterification procedure in analogy to the oxidative cleavage−esterification of furans.[13] In the first step, pyrrole **16** was oxidized to the derived carboxylic acid, which then was converted into the known methyl ester **17** (eq 2).



16 **17**

By comparison of the optical rotation, the absolute stereochemistry of the prepared compound was thus determined to be of the *S*-configuration. The catalytic cycle depicted in Scheme 1 also nicely accounts for this absolute configuration.

In conclusion, we have demonstrated the use of dinuclear zinc bis-ProPhenol complex **1** in an atom economic Friedel−Crafts reaction of unprotected pyrroles with a variety of differently substituted nitroalkenes to give both mono- and disubstituted pyrroles. The reactions shown gave excellent stereoselectivities in most cases. Tandem atom economic addition reactions to form 2,5-disubstituted pyrroles were also demonstrated. Further the avoidance of using *N*-protecting groups in pyrrole alkylations also enhances the efficiency by which substituted pyrroles may be synthesized. Further investigations concerning the scope of the dinuclear zinc complex are under way in our group.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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