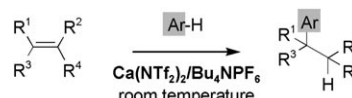


Calcium-Catalyzed Hydroarylation of Alkenes at Room Temperature

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Elaboration of simple olefins represents one of the most fundamental transformations for the synthesis of commodity chemicals and pharmacologically relevant target molecules.^[1] In this context, the formal addition of a nucleophile HX across a C–C double bond to form a functionalized alkane is an ideal chemical process, that has attracted considerable scientific commitment in the past.^[2] Transition-metal,^[3] Brønsted,^[4] or Lewis acid^[5] catalysts were employed for hydrofunctionalizations with amine,^[6] alcohol,^[2,7] and activated methylene^[8,9] nucleophiles. Reactions of olefinic double bonds with electron-rich aromatic compounds are especially interesting,^[10–13] as they combine the benefits of olefin hydrofunctionalizations with a C–H transformation of an aromatic compound. Furthermore, these so-called hydroarylation processes can be considered as an atom economical alternative to classical Friedel–Crafts-type alkylations of arenes.^[11]

Nowadays the development of sustainable methods using abundant and cheap catalysts becomes more and more important. Precious metals, which still play a fundamental role as the central metal of homogeneous catalysts, are expensive and are becoming increasingly rare as we use up the Nature's resources. Surprisingly, the elaboration of main group metal catalyzed reactions has received very little attention in the past. Among other alkaline earth metals, calcium seems to be an ideal candidate,^[14] as it is essentially non-toxic, very cheap, and one of the most abundant elements in the earth crust. Recently, our group demonstrated the efficiency of a novel calcium-based catalytic system for the addition of benzylic, allylic, and propargylic alcohols to arenes and heteroarenes under very mild reaction conditions (Scheme 1).^[15] Herein, we present that the Lewis acidic properties of the same catalytic system promote the addition of electron-rich arenes across C–C double bonds, thus offer-

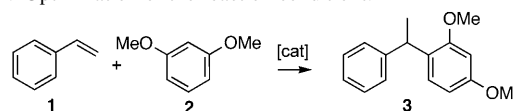


Scheme 1. Calcium-catalyzed hydroarylation of olefins.

ing an even easier access to synthetically useful aryl-substituted compounds. The hydroarylation of di- and trisubstituted styrenes, cyclic and linear dienes as well as cyclic trisubstituted alkenes was found to proceed smoothly at room temperature in the presence of the calcium-based catalyst system and full conversion was obtained within 30 min to a few hours. Thus, due to the very mild reaction conditions, the new catalyst appears suitable to address some of the typical limitations of hydroarylation reactions, such as low functional group tolerance and narrow substrate scope.

Initially the Ca(NTf₂)₂/Bu₄NPF₆ catalytic system was applied to the hydroarylation of styrene **1** with resorcinol dimethyl ether **2** as model substrates. The comparison with various other Lewis and Brønsted acids clearly demonstrated the outstanding catalytic potential of the calcium catalyst (Table 1). Furthermore, the catalyst loading could be lowered to 2.5 mol% without significant loss of catalytic activi-

Table 1. Optimization of the reaction conditions.



| Entry ^[a] | (Lewis-) acid [mol %] | Additive [mol %] | t [h] | Yield ^[b] [%] |
|----------------------|--|--|------------|--------------------------|
| 2 | Mg(NTf ₂) ₂ (5) | Bu ₄ NPF ₆ (5) | 16 | – |
| 3 | Ca(NTf₂)₂ (5) | Bu₄NPF₆ (5) | 0.2 | 91 |
| 3 | Ca(NTf₂)₂ (2.5) | Bu₄NPF₆ (2.5) | 0.5 | 89 |
| 4 | Ba(NTf ₂) ₂ (5) | Bu ₄ NPF ₆ (5) | 16 | 15 |
| 5 | Ca(NTf ₂) ₂ (5) | – | 16 | – |
| 6 | Ca(OTf) ₂ (5) | Bu ₄ NPF ₆ (5) | 16 | 52 |
| 8 | HNTf ₂ (5) | Bu ₄ NPF ₆ (5) | 16 | 45 |
| 10 | HOTf (5) | Bu ₄ NPF ₆ (5) | 16 | 35 |

[a] 5 mol% Additive and 5 mol% Lewis acid were added at room temperature to the alkene (0.5 mmol) and arene **2** (1.5 mmol) in CH₂Cl₂ (1 mL) and stirred for the time indicated. [b] Isolated yield.

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ty. In accordance with our previous findings, the 1:1 stoichiometry of the calcium salt and the hexafluorophosphate was critical for an efficient conversion. This indicates that an anion exchange might take place to form a more reactive $\text{CaNTf}_2 \cdot \text{PF}_6$ species.^[15,16] Suitable solvents were aprotic and non-coordinating, such as dichloromethane, dichloroethane or hexane. As in our previous findings for the reaction of arenes with alcohols, the observed regioselectivity of the aromatic alkylation was found to be remarkable. Attack of the olefinic electrophile occurred exclusively in *o,p*-position to the residual methoxy groups of resorcinol dimethyl ether **2**.^[17] We observed insignificant overalkylation in the presence of three equivalents of the arene.

To explore the scope of the reaction a series of differently substituted styrenes was reacted with resorcinol dimethyl ether **2** (Table 2). With 2.5 mol % of $\text{Ca}(\text{NTf}_2)_2/\text{Bu}_4\text{NPF}_6$ full

is known for styrenes bearing an electron-withdrawing substituent in the 2-position.^[13] Electron-rich phenylpropenes, such as isoeugenol (entry 3), were found to react exclusively at the α -position. Interestingly, no isomerization of the double bond in the methyl indenenes (entry 7,8) was observed. Lower yields for entries 3,7, and 8 are due to a background reaction yielding small amounts of homocoupled products. Even though a much longer reaction time was required to achieve full conversion of phenylcyclohexene (entry 9), the desired product was formed selectively in a good yield. To our knowledge this is the first time that a substrate with such a high degree of steric congestion was successfully transformed in a hydroarylation reaction. Encouraged by this result we turned our attention toward the transformation of less reactive alkenes without α -phenyl substituents (Table 3).

Table 2. Reaction of resorcinol dimethyl ether **2** with styrenes.

| Entry ^[a] | Alkene | Product ^[b] | <i>t</i> [h] | Yield ^[c] [%] | |
|----------------------|--------|------------------------|--------------|--------------------------|-------------------|
| 1 | | | 4 | 0.5 | 95 |
| 2 | | | 5 | 2 | 92 |
| 3 | | | 6 | 0.5 | 86 |
| 4 | | | 7 | 2 | 78 ^[d] |
| 5 | | | 8 | 1 | 89 |
| 6 | | | 9 | 0.5 | 92 |
| 7 | | | 10 | 0.5 | 72 |
| 8 | | | 11 | 0.5 | 76 |
| 9 | | | 12 | 12 | 65 |

[a] 2.5 mol % Bu_4NPF_6 and 2.5 mol % $\text{Ca}(\text{NTf}_2)_2$ were added at room temperature to styrene (0.5 mmol) and arene **2** (1.5 mmol) in CH_2Cl_2 (1 mL) and stirred for the time indicated. [b] Ar: *o,p*-dimethoxyphenyl. [c] Isolated yield. [d] 10:1 mixture of regioisomers (*o,p*- vs *o,o*-substitution).

conversion of the styrene was usually achieved after 30 min to 2 h and the corresponding diarylalkane products **4–10** were obtained in 72–95 % yield. α -Substituted (entry 1,2, 5, 8–9) as well as electron-withdrawing halo-substituents bearing styrenes (entry 4–5) were readily hydroarylated, even though both substrate groups are considered to be poorly reactive. Regioselectivities were generally excellent, only the reaction of 2-fluorostyrene (entry 4) gave a 10:1 mixture of isomers (*o,p*- vs *o,o*-substitution). This drop in selectivity

Table 3. Reaction of resorcinol dimethyl ether **2** with alkenes.

| Entry ^[a] | Alkene | Product ^[b] | <i>t</i> [h] | Yield ^[c] [%] | |
|----------------------|--------|------------------------|--------------|--------------------------|----|
| 1 | | | 13 | 0.5 | 72 |
| 2 | | | 14 | 0.5 | 75 |
| 3 | | | 15 | 0.5 | 83 |
| 4 | | | 16 | 0.5 | 87 |
| 5 | | | 17 | 0.5 | 84 |
| 6 ^[d] | | | 18 | 2 | 92 |
| 7 ^[d] | | | 19 | 6 | 89 |
| 8 ^[d] | | | 20 | 2 | 91 |

[a] 2.5 mol % Bu_4NPF_6 and 2.5 mol % $\text{Ca}(\text{NTf}_2)_2$ were added at room temperature to the alkene (0.5 mmol) and arene **2** (1.5 mmol) in CH_2Cl_2 (1 mL) and stirred for the time indicated. [b] Ar: *o,p*-dimethoxyphenyl. [c] isolated yield. [d] 5 mol % Bu_4NPF_6 and 5 mol % $\text{Ca}(\text{NTf}_2)_2$ were used.

The reaction of resorcinol dimethyl ether **2** with cyclic and acyclic dienes (entries 1–5) proceeded smoothly in the presence of 2.5 mol % of the calcium-catalyst. Nucleophilic attack of the arene occurred exclusively at the 3-position of the cyclic dienes (entry 1,2). In like manner, conversion of 1,3-pentadiene (entry 3) gave the mono-arylated product **15**. A second arylation was not observed for the cyclic dienes or for 1,3-pentadiene even upon heating of the reaction mixtures up to 130 °C (microwave irradiation). However, subjecting isoprene or methylpentadiene (entry 4,5) to the reaction conditions gave full conversion to the bisarylated products **16** and **17** after 30 min at room temperature. Attempts to isolate the monoarylated product by shortening the reaction time or lowering the catalyst loading were unsuccessful. Changing the stoichiometry, thus lowering the amount of arene, resulted in the formation of complex mixtures of bis-

arylated and cyclized products, formed by intramolecular reaction pathways.

When cyclic trisubstituted alkenes were treated with resorcinol dimethyl ether, hydroarylation products **18–20** were obtained selectively. Due to the inferior reactivity of these compounds a slightly higher catalyst concentration of 5 mol% was required to achieve full conversion.

To further evaluate the scope of the hydroarylation reaction, a series of different arenes and heteroarenes was added to α -methylstyrene (Table 4). This substrate was chosen as general investigations of its reactivity toward different coupling partners are scarce, due to its rather unreactive nature in this type of reaction. We were pleased to find that hydroarylation occurred readily with electron-rich aromatic compounds at room temperature giving the desired products in good to excellent yields with exceptionally high *p*-selectivity in all cases.^[17]

Table 4. Hydroarylation of α -methylstyrene with different arenes and heteroarenes.

| Entry ^[a] | Arene | Product ^[b] | <i>t</i> [h] | Yield ^[c] [%] |
|----------------------|-------|------------------------|--------------|--------------------------|
| 1 | | | 0.5 | 91 |
| 2 | | | 0.5 | 82 |
| 3 | | | 0.5 | 87 |
| 4 | | | 0.5 | 75 |
| 5 | | | 0.5 | 81 |
| 6 | | | 1 | 86 |

[a] 2.5 mol% Bu₄NPF₆ and 2.5 mol% Ca(NTf₂)₂ were added at room temperature to the alkene (0.5 mmol) and arene **17** (1.5 mmol) in CH₂Cl₂ (1 mL) and stirred for the time indicated. [b] Ar: *o,p*-dimethoxyphenyl. [c] Isolated yield.

Preliminary mechanistic investigations were undertaken to address the question whether the reactive carbocationic intermediate is generated directly by the reversible addition of a Lewis acid to the olefinic double bond or proceeds via a carbinol formed in situ through the addition of adventitious water as envisioned in our previous publication.^[17]

Competition experiments showed that an alcoholic substrate, such as phenyl ethanol, is consumed with high preference in the presence of a corresponding olefin such as styrene (see Figure 1). Additionally, the model reaction of styrene **1** with resorcinol dimethyl ether **2** was inhibited when run under strictly moisture free conditions. These findings suggest that the reaction proceeds via the formation of the carbinol, even though such an intermediate was undetecta-

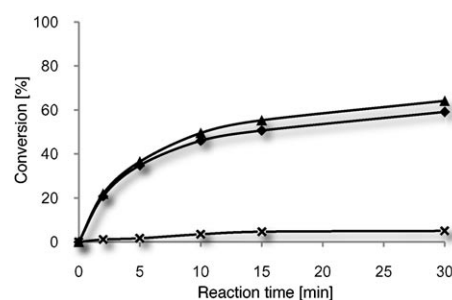


Figure 1. Conversion of phenylethanol with resorcinol dimethyl ether **2** in the presence of styrene **1** (♦: consumption^[a] of phenylethanol; ×: consumption^[a] of styrene; ▲: formation^[a] of diarylmethane **3**; [a] determined by GC analysis).

ble in the reaction mixture by GC and NMR analysis at any time. Further investigations are currently in progress in our laboratories to elucidate the mechanism of the reaction.

In conclusion, a highly efficient calcium-catalyzed intermolecular hydroarylation reaction of aryl and aliphatic alkenes has been developed. A variety of electron-poor, electron-rich, and trisubstituted styrene derivatives was converted into the desired diarylalkanes within less than an hour at room temperature. Additionally, dienes and even trisubstituted olefins were readily arylated, due to the high reactivity of the Ca(NTf₂)₂/Bu₄NPF₆ catalytic system. Free phenolic hydroxyl groups, acetates, furans, and thiophenes are tolerated under the very mild reaction conditions. Typical reactions proceed at room temperature and no special precautions for exclusion of moisture or air are necessary.

Experimental Section

Synthesis of compound 3: Styrene (52 mg, 0.5 mmol) and resorcinol dimethyl ether (207 mg, 1.5 mmol) were dissolved in dichloromethane (1 mL). Bu₄NPF₆ (5 mg, 2.5 mol%) and Ca(NTf₂)₂ (7.5 mg, 2.5 mol%) were added at room temperature and the reaction mixture is stirred for 30 min. For the isolation of the product, a satd. NaHCO₃ solution (5 mL) was added, the aqueous phase was extracted with dichloromethane, the combined organic phases dried over Na₂SO₄ and concentrated in vacuo. The crude product was purified by column chromatography (107 mg, 89%).

Keywords: alkenes • arenes • calcium • Friedel–Crafts alkylation • hydroarylation

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