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Room Temperature Catalyst System for the Hydroarylation of Olefins

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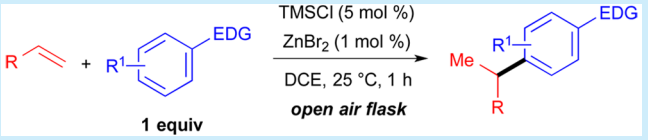
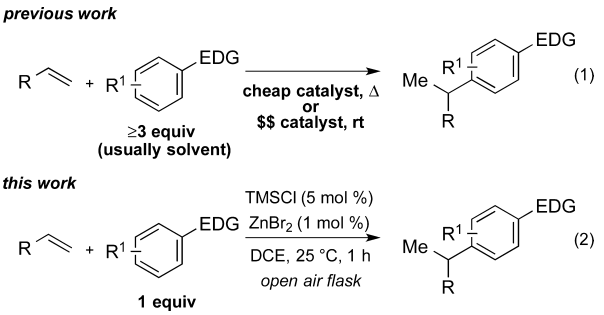
Supporting Information

ABSTRACT: A simple protocol for the hydroarylation of olefins to yield diarylmethine products is described. A Friedel–Crafts-type synthetic strategy allows direct access to biorelevant products in high atom efficiency. A combination of substoichiometric amounts of TMSCl and $ZnBr_2$ promotes a rapid hydroarylation process at ambient temperature. The method is high yielding and is amenable to scale-up protocols.



Alkyl arenes are an important structural motif in various materials, pharmaceuticals, and fine chemicals.[1] In particular, diarylmethines represent privileged scaffolds in therapeutic development.[2] Traditional methods to access diarylmethines include olefin hydrogenation[3] and Friedel–Crafts alkylation using alkyl halide electrophiles.[4] Hydroarylation of olefins represents an atom-efficient Friedel–Crafts alkylation reaction that employs simple organic building blocks. Currently, two synthetic tactics are known to achieve the hydroarylation of olefins: Friedel–Crafts alkylation and transition metal catalysis.[5] The Friedel–Crafts method has been realized with $AlCl_3$,[1] $FeCl_3$,[6] bismuth reagents,[7] gold complexes,[8] and graphene oxide (Scheme 1, eq 1).[9] In addition, Brønsted acids,[10] including acidic

Scheme 1. Mild Conditions for the Hydroarylation of Olefins



resins[11] and zeolites,[12] are capable of achieving the hydroarylation of olefins. Major drawbacks of these procedures include high temperatures,[1,6−11,12b] polyalkylation,[1a] stoichiometric amounts of Lewis acid,[1a] and requirement of the arene in excess (commonly as solvent).[6−11,12b] A room temperature hydroarylation was achieved by Niggemann and co-workers[13] using $Ca(NTf_2)_2$ with Bu_4NPF_6; however, this reagent combination is expensive and also requires excess arene. Stephan and co-workers reported an elegant advance in this area; however, the phosphonium cation catalyst requires multiple steps to produce.[14] The alternative tactic using transition metal catalysts such as Ru,[15] Ir,[16] Pt,[17] and Pd/Cu[18] provides hydroarylated products with a high degree of regio- and chemoselectivity; however, these methods require expensive, toxic metals and generally harsh reaction conditions. Importantly, the transition metal route also proceeds to yield the anti-Markovnikov products. Our laboratory's interest in atom-efficient functionalizations of π-systems[19] prompted us to explore a strategy to generate diarylmethines through the hydroarylation of styrene derivatives. To address the shortcomings of previous reports, we searched for a low-cost, mild method for the hydroarylation of styrene derivatives. We were primarily interested in developing a Lewis acid system that could perform the hydroarylation at ambient temperature while using equivalent stoichiometry of styrene and arene. Based on previous success in carbon–carbon bond-forming reactions, we focused our attention on the use of silicon halides along with an additive.[20] Herein, we report a TMSCl/$ZnBr_2$ cocatalyst system for the mild hydroarylation of styrene (Scheme 1, eq 2). To the best of our knowledge, there are currently no known reports of olefin functionalization using this catalyst system.

Hydroarylation of styrene with anisole was first explored using trimethylsilyl chloride (TMSCl) in combination with various metal salts (see Supporting Information, Table SI-1). We observed that zinc salts afforded the highest conversion and yield of hydroarylation products (Table 1). The employment of zinc dust provided the highest yield of hydroarylation product **1a** (entry 1). Zinc chloride and zinc bromide provided similar yield and conversion to the hydroarylation products (entries 2 and 3). After surveying multiple reactions using Zn, $ZnCl_2$, and $ZnBr_2$ in parallel, we observed that Zn and $ZnCl_2$ produced inconsistent reaction conditions. Therefore, we chose $ZnBr_2$ as our optimal cocatalyst for further screening. Examining the stoichiometry and catalyst loading determined that TMSCl/$ZnBr_2$ is optimal at 5:1 based on entries 4–6. Removal of either TMSCl or $ZnBr_2$ provided no reactivity, which demonstrates the necessity for each reagent in the hydroarylation (entries 7 and 8). Finally, we screened various halosilanes (see Supporting Information Table

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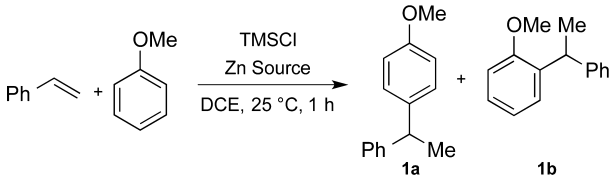
Table 1. Optimization of Catalytic Conditions[a]



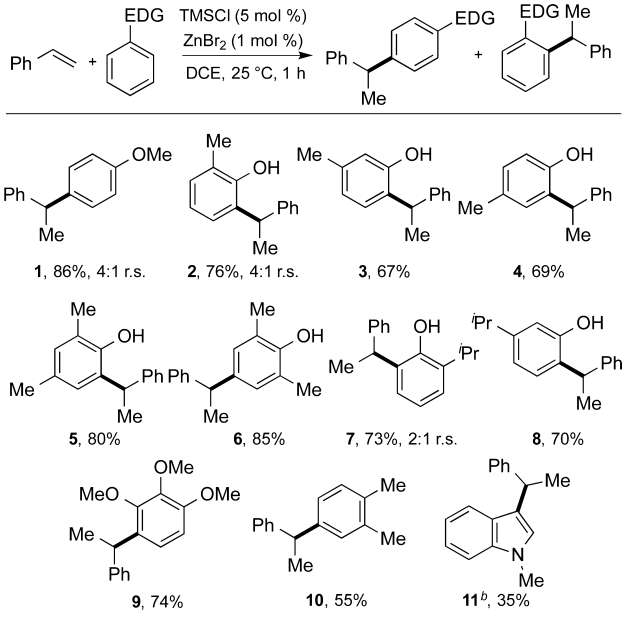
entry	TMSCl (mol %)	Zn source (mol %)	yield of **1a** (%)	yield of **1b** (%)
1	10	Zn (2)	78	12
2	10	$ZnCl_2$ (2)	72	14
3	10	$ZnBr_2$ (2)	75	16
4	**5**	**$ZnBr_2$ (1)**	**76**	**15**
5	2	$ZnBr_2$ (1)	45	9
6	1	$ZnBr_2$ (1)	35	7
7	10		0	0
8		$ZnBr_2$ (1)	0	0

[a]Yield was determined by uncalibrated GC/MS analysis of the crude reaction mixture relative to an internal standard.

SI-2) and chose TMSCl as the optimal catalyst due to lower cost and ease of use.

With the optimized reaction conditions, we investigated the scope of the hydroarylation of styrene with electron-rich arenes (Scheme 2). Methylated phenols with different substitution

Scheme 2. Substrate Scope of Various Arenes with Styrene[a]



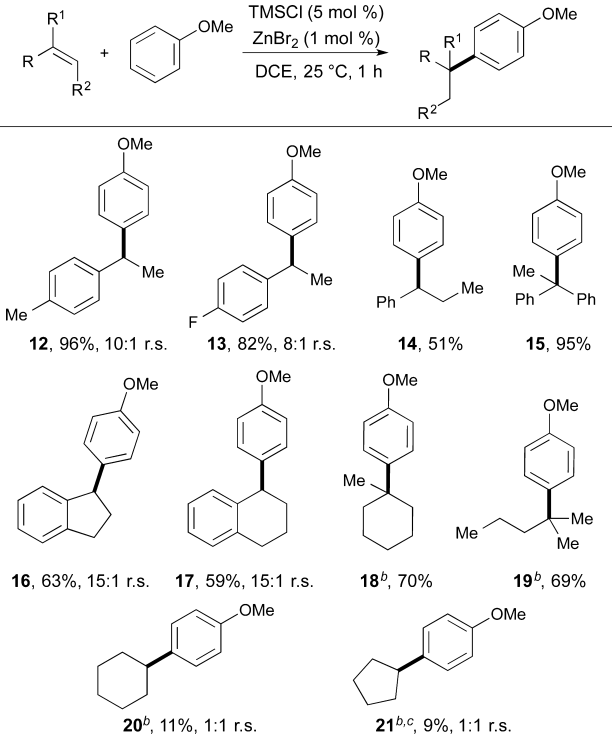
[a]Isolated yields are reported as an average of two 0.9 mmol scale reactions. Regioselectivity (r.s.) was determined by ^{1}H NMR analysis of the isolated material. [b]Reaction performed in 2-methyltetrahydrofuran at 90 °C.

patterns were capable of producing hydroarylation products **2**–**6** in good to excellent yields. Phenols with 2-isopropyl or 3-isopropyl groups proceeded to give 73% of **7** and 70% of **8**, respectively. Good yield was observed using 1,2,3-trimethoxybenzene, affording 74% of **9** as a single regioisomer. Interestingly, *o*-xylene was efficient at producing the hydroarylation product **10** in 55% yield under our optimized conditions at 1:1 stoichiometry of *o*-xylene/styrene. Xylene substrates are less nucleophilic and often require the xylene to be used in large excess for efficient reactivity.[6,7] Notably, complete regioselectivity was observed in the production of **3**, **8**, **9**, **10**, and **11**. Mixtures of regioisomers were obtained with products **1**, **2**, and **7**, which is consistent with other Friedel–Crafts systems.[6,7,8a,9−12]

Alkylation of indoles using a hydroarylation strategy has observed significant advances in recent years[8b] as alkylated indoles are a common structural motif in biorelevant compounds.[21] Unfortunately, we did not observe the hydroarylation product under our standard conditions. A brief screen of modified conditions revealed that 2-methyltetrahydrofuran as the solvent at an increased temperature provides the hydroarylation product of styrene with *N*-methylindole in a 35% yield (product **11**).

To expand the scope of this hydroarylation strategy, we also surveyed the hydroarylation of other olefins with anisole under the optimized conditions (Scheme 3). Substitution on the phenyl

Scheme 3. Scope of Substituted Olefins with Anisole[a]



[a]Isolated yields are reported as an average of two 0.9 mmol scale reactions. Regioselectivity (r.s.) was determined by ^{1}H NMR analysis of the isolated material. [b]Reaction performed with 5 equiv of anisole. [c]Yield reported is based on GC analysis relative to an internal standard.

ring of styrene was well-tolerated and provided the hydroarylation products in good yield and regioselectivity (**12**, **13**, **16**, and **17**). Both α- and β-substituted styrenes provided good to excellent isolated yields and high regioselectivity (**14** and **15**). Non-styrenyl substrates are rarely reported for the hydroarylation process,[6−9,11,12] with the exception of reports by Bergman,[10a] Doye,[10b] Niggemann,[13] and Stephan.[14] Employing equivalent stoichiometry of anisole and alkyl olefin unfortunately provided the hydroarylated products in low yield. Increasing the amount of anisole provided a more efficient reaction, with trisubstituted olefins giving 70% yield of **18** and 69% yield of **19**.

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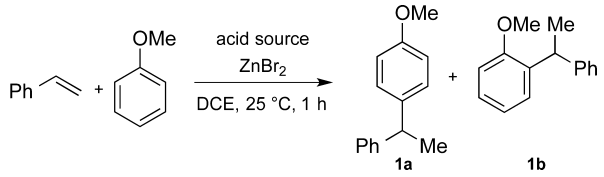
Hydroarylation of cyclohexene and cyclopentene provided low yields of the products (**20** and **21**).

Our optimized conditions were ineffective when employing substrates with basic functional groups (i.e., pyridyl), which prompted us to probe the mechanism of the reaction (Table 2).

Table 2. Mechanistic Probe[a]



entry	acid source (mol %)	$ZnBr_2$ (mol %)	yield of **1a** (%)	yield of **1b** (%)
1[b]	TMSCl (5)	1	0	0
2[c]	TMSCl (5)	1	0	0
3[d]	TMSCl (5)	1	0	0
4	HCl(g)	1	80	12
5	HCl(g)		0	0

[a]Yield was determined by uncalibrated GC/MS analysis of the crude reaction mixture relative to an internal standard. [b]Reaction performed with 5 mol % of di-*tert*-butylpyridine. [c]Reaction performed with 1 equiv of K_2CO_3. [d]Reaction performed with 10 mol % of pyridine at 60 °C.

Utilizing bases such as 2,6-di-*tert*-butylpyridine, potassium carbonate, and pyridine completely disrupted any reactivity (entries 1−3). Increased temperatures under basic conditions were also ineffective at promoting the reaction (entry 3). Removal of the TMSCl and introduction of gaseous HCl provided comparable results to our optimized conditions (entry 4); however, HCl(g) alone did not provide the hydroarylation products (entry 5). In addition, other Brønsted acids were tested and afforded the products with diminished yields compared to our optimized conditions (see Supporting Information Table SI-3). These combined results suggest that the TMSCl/$ZnBr_2$ cocatalyst system likely operates through both a Brønsted acid and Lewis acid mechanism. The TMSCl presumably releases HCl to act as the Brønsted acid; however, the Lewis acidic $ZnBr_2$ is required to complete the reaction.[22] Further investigations to determine the mechanism and the identity of the active catalyst are currently underway and will be reported in due course.

Finally, to demonstrate the practicality of this process, the scale of the hydroarylation reaction was increased. On a 5 g scale, the hydroarylation of styrene with 2,6-dimethylphenol gave product **6** in 82% yield (Scheme 4). This yield is comparable to the small-scale reaction in Scheme 2, which demonstrates that the process is scalable.

In conclusion, we have developed a low-cost, mild, and scalable catalyst system for the efficient hydroarylation of olefins. Our method provides valuable diarylmethine products in good to excellent yields while avoiding harsh conditions and wasteful use of reagents. We are currently performing mechanistic studies in an effort to elucidate the active catalyst and reactive intermediates.

Scheme 4. Scaled-up Hydroarylation Reaction

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02492.

Experimental details, characterization data, and NMR spectra for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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