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A highly efficient gold/silver-catalyzed addition of arenes to imines

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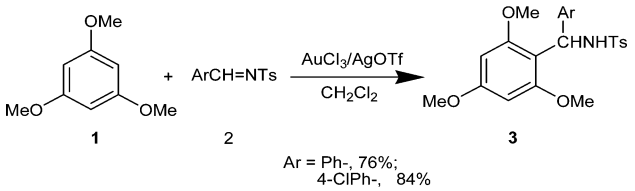
A highly efficient imino Friedel–Crafts type addition of arenes to imines is developed by using a combination of gold and silver catalysts; various amino acid derivatives are generated by this method.

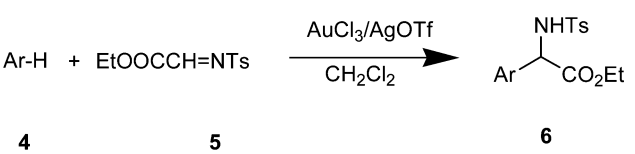
The biological importance of proteins and peptides has led to the continuous search for new methods for the synthesis of chiral and achiral α-amino acid derivatives.[1] The use of glyoxylate imines provides access to various non-proteinogenic α-amino acids through ene reactions,[2] cycloaddition reactions,[3] radical additions,[4] and nucleophilic additions.[5] There have been extensive studies on catalytic or stoichiometric Friedel–Crafts reactions.[6] However, the related imino Friedel–Crafts reactions between imines and aromatic systems have been very limited due to the lower reactivities of imines.[7] As part of our continued interest in developing new methods for synthesizing amino acids,[8] we recently reported an example of an imino Friedel–Crafts reaction between phenols and glyoxylate-derived imines catalyzed by lanthanide triflates.[9] Independently, Wang and co-workers reported a similar reaction mediated and catalyzed by $TiCl_4$.[10] However, in both cases, the reactions are limited to unprotected phenols. No appreciable reaction was observed with common arenes. For such arenes, the nucleophilic addition reactions using arylorganometallics derivatives with or without transition-metals are generally used.[11] It is highly desirable to develop methods to generate amino acid derivatives *via* direct and general arene–imine additions. Herein, we wish to report such a synthesis through an imino Friedel–Crafts reaction catalyzed by gold/silver.



Scheme 1

Table 1 Catalyst optimization for the imino Friedel–Crafts reaction of 1,3,5-trimethoxybenzene and imine **2**

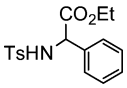
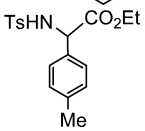
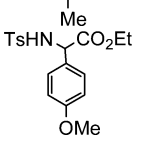
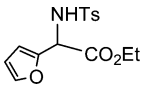
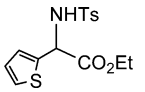
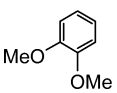
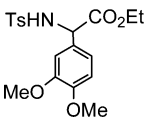
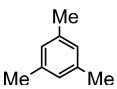
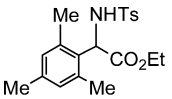
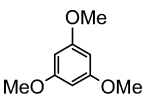
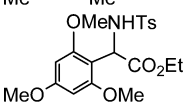
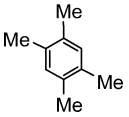
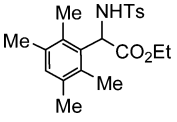
Entry	Catalyst	Yield (%)
1	$AuBr_3$/AgOTf	53
2	$AuCl_3$/AgOTf	84
3	$ZnCl_2$	No reaction
4	$AlCl_3$	No reaction
5	$RuCl_3 \cdot 3H_2O$	No reaction
6	AgOTf	49
7	$AuCl_3$	64



Scheme 2

To begin our study, we examined the reaction of an electron-rich arene with a readily available imine (Scheme 1). Recently, gold[12] and silver[13] have been found to have interesting catalytic activities. Following our studies on gold[14] and silver[15] catalyzed reactions of terminal alkynes, and a novel nucleophilic addition of activated methylene compounds to alkene,[16] we envisioned the potential application of such catalytic systems for the synthetically desired imino Friedel–Crafts reactions. Initially, 1,3,5-trimethoxybenzene (**1**) was reacted with phenyl-*N*-tosylmethanimine (**2**) in methylene chloride by using several potential catalysts such as $ZnCl_2$, $AlCl_3$, and $RuCl_3 \cdot 3H_2O$ (Table 1). However, no reaction was observed in most cases. When a combination of $AuBr_3$/AgOTf was used, the desired aromatic amine (**3**) product was obtained in 53% yield. The change of $AuBr_3$ to $AuCl_3$ improved the yield to 84%. When

Table 2 Amino acid synthesis *via* imino Friedel–Crafts type reactions catalyzed by gold/silver

Entry	Ar–H	Temperature/°C[a]	Product	Yield (%)[b]
1[c]		80		34
2		50		77 (p : o = 81 : 19)[d]
3		50		80
4		0		73
5		0		60
6		0		80
7		0		84
8		0		85
9		0		72

[a] Oil bath/bath temperature. [b] Isolated yield after flash chromatography. [c] 2 mL benzene was used as solvent. [d] Determined by GC-MS.

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AgOTf was used as the catalyst, the reaction was also effective and generated the desired product in 49% yield under similar reaction conditions; whereas the use of $AuCl_3$ alone as the catalyst led to the product in 64% yield. The yield was slightly increased when chlorophenyl-*N*-tosylmethanimine was used (Scheme 1).

Subsequently, various arenes **4** were reacted with imine **5** generated from glyoxylate and *p*-toluenesulfonamide (Scheme 2). Various amino acid derivatives **6** were obtained by using the $AuCl_3$/AgOTf catalyzed imino Friedel–Crafts type reaction. Both aromatic and heteromatic compounds are effective under the current reaction conditions (Table 2). Surprisingly, highly electron-rich indole did not react under the present reaction conditions. In contrast, in previous catalytic systems, only special arenes, such as phenol, indole, were successful. In the current catalytic system, the reaction of a variety of arenes including benzene or toluene and α-amino ester proceeded in good yields (Table 2).[17]

In conclusion, an efficient gold/silver-catalyzed imino Friedel–Crafts reaction was developed. A variety of amino acid derivatives were synthesized by the method. The process is simple and can be used to generate a wide range of electron-rich arenes. The scope, mechanism, and synthetic applications *via* this reaction are under investigation.

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17 General experimental procedure: To a solution of the arene (1 mmol) and imine (1 mmol) in 3 mL CH_2Cl_2 was added $AuCl_3$ (0.02 mmol, 2 mol%) and AgOTf (0.06 mmol, 6 mol%) under an air atmosphere. The reaction mixture was capped and stirred for 12 h. The solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (eluent hexane : ethyl acetate = 4 : 1) to afford the aromatic amine.