Homogeneous Catalysis

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A Copper(II)-Catalyzed Aza-Friedel–Crafts Reaction of *N*-(2-Pyridyl)sulfonyl Aldimines: Synthesis of Unsymmetrical Diaryl Amines and Triaryl Methanes**

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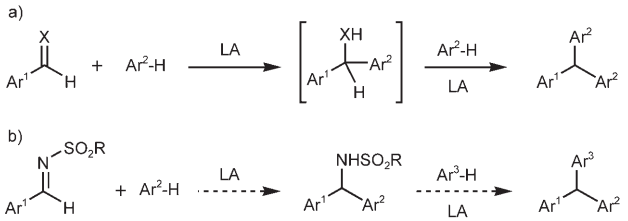
The Lewis acid-catalyzed addition of electron-rich aromatic compounds to aldehydes, ketones and imines, the latter of which is known as the aza-Friedel–Crafts reaction (AFCR), is a synthetically outstanding C–C bond-forming process that leads to functionalized alcohols and amines in a completely atom-economical way.[1] However, despite its significance, a number of unsolved aspects related to functional-group tolerance, either with regard to the arene nucleophile or the electrophilic substrate, still remain for this transformation. For instance, the mono Friedel–Crafts reaction of carbonyl compounds and imines seems to be restricted to highly electrophilic substrates[2] such as glyoxylates,[3] chloral (trichloroacetaldehyde),[4] pyruvates,[5] trifluoromethyl imines,[6] or α-imino esters.[3c,7] In contrast, aromatic aldehydes[8] and their imines,[3c,9] generally evolve according to a double Friedel–Crafts reaction to give symmetrical triaryl methanes due to the intrinsic instability of the intermediate benzylic alcohol (or amine derivative) under the acidic reaction conditions (Scheme 1a). Triaryl methanes display varied and interesting properties and have received a great deal of attention as leuco dyes,[10] photochromic agents,[11] suitable building blocks for generating dendrimers,[12] and as substrates for theoretical[13] and biological[14] studies. While many methods have been reported for the preparation of symmetrical triaryl methanes,[15] the synthesis of unsymmetrical derivatives is much less developed.[16,17]

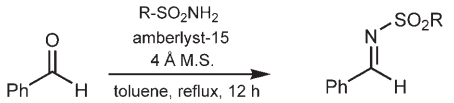


Scheme 1. Synthesis of triaryl methanes from aromatic aldehydes or their imines by a Friedel–Crafts reaction. X = O, NR; LA = Lewis acid; see text for details.

As part of an ongoing research program on metal-controlled reactions of appropriately functionalized *N*-sulfonyl imines,[18] we describe here a broad-scope AFCR protocol that allows the selective preparation of structurally diverse unsymmetrical diaryl amines and triaryl methanes by sequential reaction with two different electron-rich aromatic compounds (Scheme 1b).

First, to study the effect of the sulfonyl substitution in AFCR, a set of sulfonyl imines, **1a–e**, of varied electronic and coordination nature were readily prepared in good chemical yields (87–94%) by direct condensation of benzaldehyde with the corresponding sulfonamide (Scheme 2).[19]

We chose the electron-rich *N*-methylindole[20] as model aromatic nucleophile for the AFCR of compounds **1**, and Cu(OTf) or $Cu(OTf)_2$ as catalytic Lewis acids[21] (10 mol%).



1a, R = Tol, 93%
1b, R = 4-$(NO_2)C_6H_4$, 90%
1c, R = 2-thienyl, 90%
1d, R = NMe_2, 94%
1e, R = 2-pyridyl, 87%

Scheme 2. Synthesis of *N*-sulfonyl imines **1a–e**. M.S. = molecular sieves.

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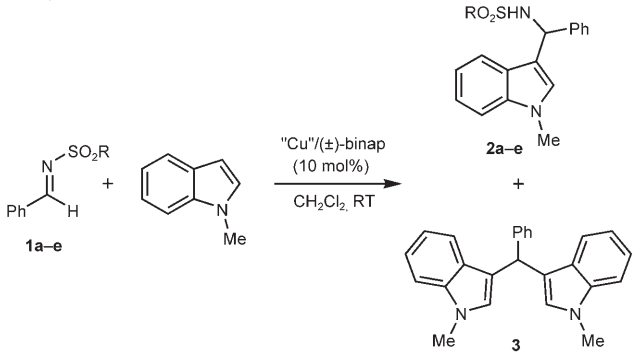
The effect of adding phosphane ligands to the reaction media was also examined [(±)-binap, dppf, dppe, and PPh_3], with binap being the most efficient.[22] The results obtained by using the optimal pair $Cu(OTf)_n$/binap (10 mol%) are summarized in Table 1.

Table 1: Cu^I- and Cu^{II}-catalyzed AFCR of sulfonyl imines **1a–e** with *N*-methylindole.



Entry	Imine	R	Copper salt	*t*	Yield [%][a] 2	3
1	**1a**	Tol	Cu(OTf)	72 h	**2a**, 41	–
2	**1a**	Tol	$Cu(OTf)_2$	≤5 min	–	72
3	**1b**	$(p\text{-}NO_2)C_6H_4$	Cu(OTf)	69 h	**2b**, 47	–
4	**1b**	$(p\text{-}NO_2)C_6H_4$	$Cu(OTf)_2$	≤5 min	–	85
5	**1c**	2-thienyl	Cu(OTf)	65 h	**2c**, 50	–
6	**1c**	2-thienyl	$Cu(OTf)_2$	≤5 min	–	80
7	**1d**	NMe_2	Cu(OTf)	70 h	**2d**, 45	–
8	**1d**	NMe_2	$Cu(OTf)_2$	≤5 min	–	82
9	**1e**	2-pyridyl	Cu(OTf)	22 h	**2e**, 72	–
10	**1e**	2-pyridyl	$Cu(OTf)_2$	≤5 min	**2e**, 72	–

[a] Yield of pure product isolated after chromatography.

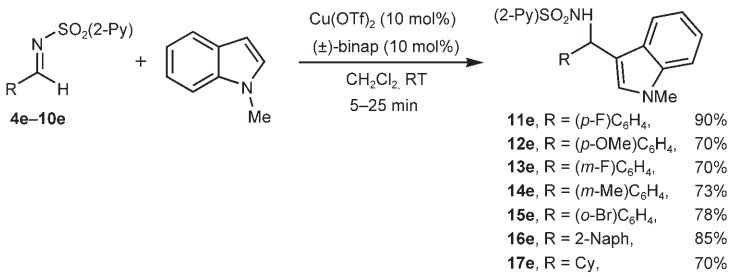
Three important conclusions can be drawn from this study:

a) The more-electrophilic Cu^{II} catalyst is around two orders on magnitude more reactive than the analogous Cu^I catalyst. For instance, the reaction of **1a** catalyzed by Cu(OTf) required 72 h to reach completion[23] (entry 1), whereas in the presence of $Cu(OTf)_2$ the reaction was complete in less than 5 min (entry 2).

b) A different outcome was obtained with substrates **1a–d** in the reactions catalyzed by either Cu(OTf) or $Cu(OTf)_2$. Thus, with the Cu^I-based protocol the mono Friedel–Crafts products **2a–d** were selectively obtained in moderate yield, while the Cu^{II} system provided selectively the bis-indole **3** in good yields (72–85%) with very short reaction times (≤5 min).

c) The 2-pyridylsulfonyl imine **1e** behaves differently to the rest of the sulfonyl imines[24] as the bis-indole product **3** is not detected either in the presence of Cu(OTf) (entry 9) or with $Cu(OTf)_2$ (entry 10).

The role of the 2-pyridylsulfonyl group in controlling the selectivity of the $Cu(OTf)_2$-catalyzed AFCR in favor of the sulfonamide product was confirmed by surveying a variety of substituted 2-pyridylsulfonyl imines. As shown in Scheme 3,



Scheme 3. Study of the substitution at the imine. Cy = cyclohexyl; Naph = naphthyl.

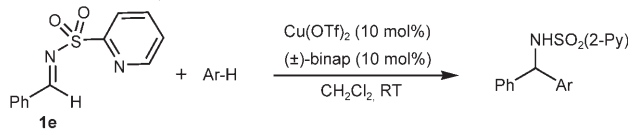
regardless of the electronic and steric nature of the substitution, the $Cu(OTf)_2$/(±)-binap-catalyzed AFCR provided exclusively the pyridylsulfonamide products **11e–17e** in good yields (70–90%). Interestingly, this method can also be applied to aliphatic imine electrophiles (product **17e**), which, to the best of our knowledge, have not been used previously in the AFCR.

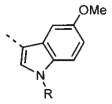
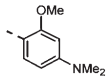
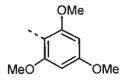
Table 2 shows the scope of the AFCR of imine **1e** with regard to the nucleophilic arene partner. Both heteroaromatic and electron-rich aromatic compounds proved to be very effective, affording the Friedel–Crafts addition product in good yield as a single regioisomer. The reactions with a representative selection of indole derivatives (entries 1–4), *N*-methylpyrrole (entry 5), 2-methoxythiophene (entry 6), and 1,3,5-trimethoxybenzene (entry 10) were particularly fast (≤5 min). Interestingly, substitution at C2 of the indole seems to have no detrimental effect on the reactivity (products **21e** and **22e**). Furan, which is known to be a poorly reactive substrate,[1e,7e] provided the addition product **26e** in 50% yield after 15 h, while the more nucleophilic 2-methoxyfuran furnished the amine **27e** in 69% yield after 90 min. Among nonheteroaromatic nucleophiles, *N*,*N*-dimethyl-3-methoxyaniline, 1-methoxynaphthalene, and 1,3,5-trimethoxybenzene also underwent the AFCR and gave satisfactory product yields (entries 8–10). However, no reaction was observed with less activated aromatic rings, such as *N*,*N*-dimethylaniline or anisole, even after prolonged reaction times.

The synthetically relevant deprotection of these pyridylsulfonamide products to give the corresponding diaryl methylamines can be cleanly achieved by treatment with magnesium turnings under neutral reaction conditions (Scheme 4).[25]

To highlight the potential of the pyridylsulfonamide adducts, we set out to develop a sequential, one-pot synthesis of unsymmetrical triaryl methanes by promoting a second electrophilic aromatic substitution with a different electron-rich arene (Ar^3-H). However, once the AFCR between imine **1e** and *N*-methylindole reached completion (monitored by TLC), the addition of 5-methoxy-1-methylindole to the formed **2e** resulted in no reaction at room temperature after 24 h. Gratifyingly, this Cu^{II}-catalyzed sulfonamide displacement proceeded smoothly when the reaction temperature was increased to 40 °C and after 20 min triaryl methane **33** was isolated in 65% yield.[26]

Table 2: Cu^{II}-catalyzed AFCR of imine **1e** with electron-rich arenes.

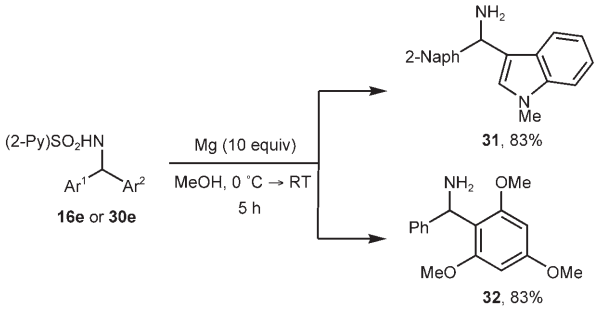


Entry	Ar	Product	*t*	Yield [%][a]
1		**2e**, R = Me **18e**, R = H	≤5 min	72 82
2		**19e**, R = H **20e**, R = Me	≤5 min	89 93
3		**21e**, R = Me **22e**, R = Ph	≤5 min	80 70
4		**23e**	≤5 min	75
5		**24e**	≤5 min	72
6		**25e**	≤5 min	65
7		**26e**, R = H **27e**, R = OMe	15 h 1.5 h	50 69
8		**28e**	8 h	73
9		**29e**	6 h	65
10		**30e**	≤5 min	76

[a] Yield of pure product isolated after chromatography.

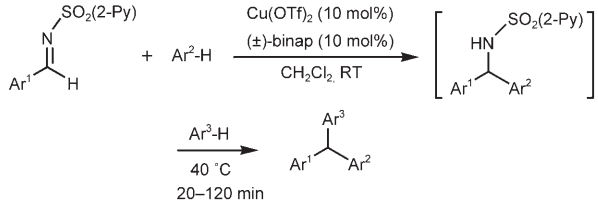
Table 3 shows the wide scope of this one-pot (indolyl)-diaryl methane synthesis with regard to the nature of the aromatic nucleophile Ar^3-H (products **33**–**40**). Even electron-rich indole derivatives (entries 1 and 4), which are known to polymerize easily under acidic conditions,[27] tolerate the mild reaction conditions.

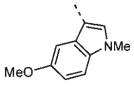
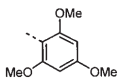
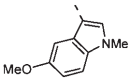
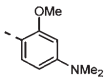
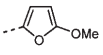
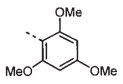
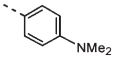
Disappointingly, this one-pot 2-pyridylsulfonamide displacement did not take place with substrates lacking an indolyl group, even under harsher conditions (DCE or CH_3CN, 60 °C). To further extend this methodology to the



Scheme 4. Deprotection of *N*-(2-pyridyl)sulfonyldiaryl amines.

Table 3: One-pot synthesis of unsymmetrical (indolyl)diaryl methanes.

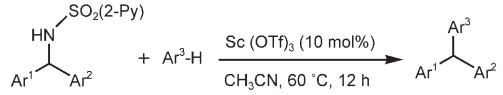


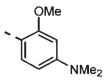
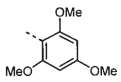
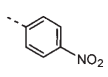
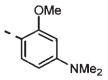
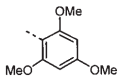
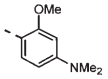
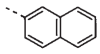
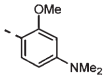
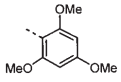
Entry	Ar^1	Ar^2	Ar^3	Product	Yield [%][a]
1				**33**	65
2				**34**	65
3				**35**	57
4				**36**	60
5				**37**	46
6				**38**	63
7				**39**	43
8				**40**	73

[a] Overall yield of pure product isolated after chromatography.

case of triaryl methanes that do not necessarily contain an indole moiety, the second electrophilic aromatic substitution was investigated with isolated sulfonamide adducts. After surveying different Lewis acids, we found that this reaction occurs cleanly in the presence of $Sc(OTf)_3$ (10 mol%) in CH_3CN at 60°C. As shown in Table 4, a variety of unsymmetrical triaryl methanes can be obtained in reasonable yields

Table 4: Synthesis of unsymmetrical triaryl methanes.



Entry	Ar^1	Ar^2	Ar^3	Product	Yield [%][a]
1				**41**	65
2				**42**	65
3				**43**	57
4				**44**	57
5				**45**	57
6				**46**	44

[a] Yield of pure product isolated after chromatography.

(44–65%) by appropriate choice of the Ar^1, Ar^2, and Ar^3 moieties. This methodology provides access to unsymmetrical triaryl methanes containing both electron-rich and electron-poor aromatic rings (e.g., products **42** and **46**), a type of compound that has seldom been studied since their synthesis has not been well established.[28]

In summary, we have developed an efficient $Cu(OTf)_2$-catalyzed AFCR of *N*-sulfonyl imines with electron-rich aromatic and heteroaromatic compounds based on the use of the 2-pyridylsulfonyl moiety as the key controlling unit. This highly reactive protocol displays a wide tolerance both with respect to the imine substrate and the arene nucleophile. In addition, this catalyst system also allows a controlled double electrophilic aromatic substitution, which provides access to unsymmetrical triaryl methanes with wide structural diversity.

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Keywords: amines · copper · homogeneous catalysis · nitrogen heterocycles · Schiff bases

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[2] To the best of our knowledge, the gold(III)-catalyzed addition of 1,3,5-trimethoxybenzene to the *N*-tosyl imines of benzaldehyde and 4-chlorobenzaldehyde,[7b] and the asymmetric organocatalytic addition of 2-methoxyfuran to aryl aldimines (D. Uraguchi, K. Sorimachi, M. Terada, *J. Am. Chem. Soc.* **2004**, *126*, 11804) are the only examples of the participation of nonactivated imines in the AFCR.

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