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Copper-assisted Wittig-type olefination of aldehydes with *p*-toluenesulfonylmethyl isocyanide†

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The Wittig reaction is a valuable and powerful tool in organic synthesis, providing a convenient route from aldehydes and ketones to alkenes. Herein, a novel copper-assisted Wittig-type olefination of aldehydes with *p*-toluenesulfonylmethyl isocyanide (TosMIC) is disclosed, providing a direct and operationally simple approach to (*E*)-vinyl sulfones under mild conditions, compatible with a multitude of common functional groups. Experimental and computational investigations imply that the reaction proceeds through an intriguing electronically-controlled (3 + 2)/retro-(3 + 2) cycloaddition pathway.

Carbon–carbon bond formation is of fundamental importance in contemporary organic synthesis. It finds application in the synthesis of biologically relevant target molecules, commodity chemicals, and materials.[1,2] Despite transition metal-catalyzed carbon–carbon bond formation being a well-established research field,[3,4] there is still great appeal in developing novel carbon–carbon coupling reactions, and even more so, for reactions producing carbon–carbon double bonds. Commercially available aldehydes and ketones are versatile building blocks in chemical synthesis and can be employed in a myriad of transformations. The properties of the carbonyl functionality allow for its application in reactions that are key to the synthetic chemists' arsenal, such as Grignard, Wittig, and aldol reactions, to name a few.[5] Of these, the Wittig reaction is one of the most efficient and streamline methodologies for converting the carbon–oxygen double bond of an aldehyde or a ketone into a new carbon–carbon double bond.[5,6] It is well-recognized that such protocols firstly undergo an intermolecular (2 + 2) cycloaddition process, in which the phosphine ylide adds to the carbonyl to form a four-membered cyclic intermediate. The intermediate is short-lived and quickly breaks down *via* a reverse (2 + 2) cycloaddition to generate the alkene.[7] Aldehydes and ketones play an irreplaceable role in this reactivity pattern. Therefore, the discovery of unprecedented coupling partners and catalysts for this reactivity is key to realizing new transformations and, subsequently, providing a lucrative springboard for diversification in chemical synthesis.

p-Toluenesulfonylmethyl isocyanide (TosMIC) is a versatile reagent that is widely used for construction of nitrogen-containing heterocyclic motifs, including oxazoles, oxazolidines, thiazoles, pyrroles, indoles, imidazoles, triazoles.[8] The structural features of this versatile reagent are of excellent utility when synthesizing organic compounds and show comprehensive chemistry with different functionalities. Recently, we disclosed copper- and silver-catalyzed heteroaromatization protocols proceeding through condensation between propargylic alcohols and TosMIC, thus revealing a conceptually novel reactivity profile of the latter.[9] Based on these findings and our continued efforts in copper- and silver-catalyzed reactions involving isocyanides,[9,10] we herein report the first example of copper-assisted Wittig-type olefination reaction of aldehydes with TosMIC *via* sequential (3 + 2) cycloaddition—retro-(3 + 2) cycloaddition (Fig. 1). Notably, this reaction provides a direct and operationally simple approach to (*E*)-vinyl sulfones with various functional groups under mild conditions from two basic chemicals. Vinyl sulfones are fruitful moieties and are key building blocks in numerous natural products and synthetic functional molecules. Furthermore, they serve as valuable intermediates in chemical synthesis and have even been found to inhibit an array of enzymatic processes, providing unique opportunities for their use in drug design and medicinal chemistry.[11,12]

Initially, 2-nitrobenzaldehyde (**1a**) and TosMIC (**2**) were selected as the model substrates to optimize the reaction conditions. The reaction of **1a** (0.6 mmol) and **2** (0.5 mmol) with 2

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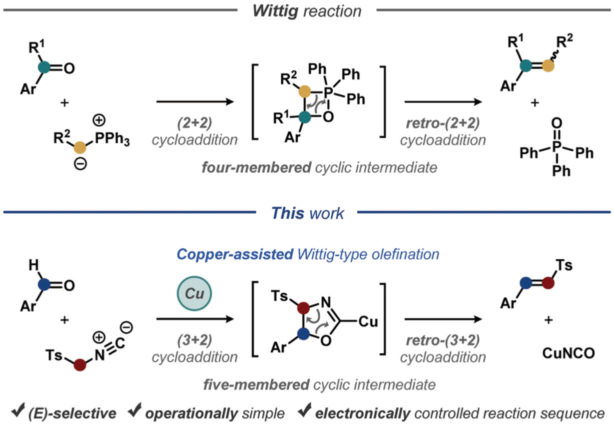
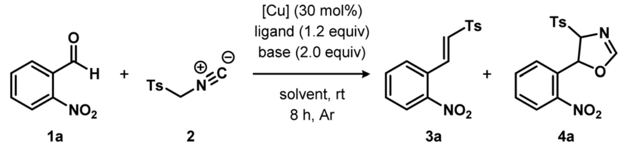


Fig. 1 Strategies for synthesis of alkenes from carbonyl-containing compounds.

equivalents of a base (K_2CO_3, Cs_2CO_3 or DBU) in *N*,*N*-dimethylformamide (DMF) at 25 °C afforded oxazole **4a** in high yields (Table 1, entries 1–3). Upon addition of CuI (30 mol%) into the reaction system, a new product, vinylsulfone **3a**, was isolated from the reaction in 13% yield (Table 1, entry 4).

Table 1 Optimization of the reaction conditions[a]



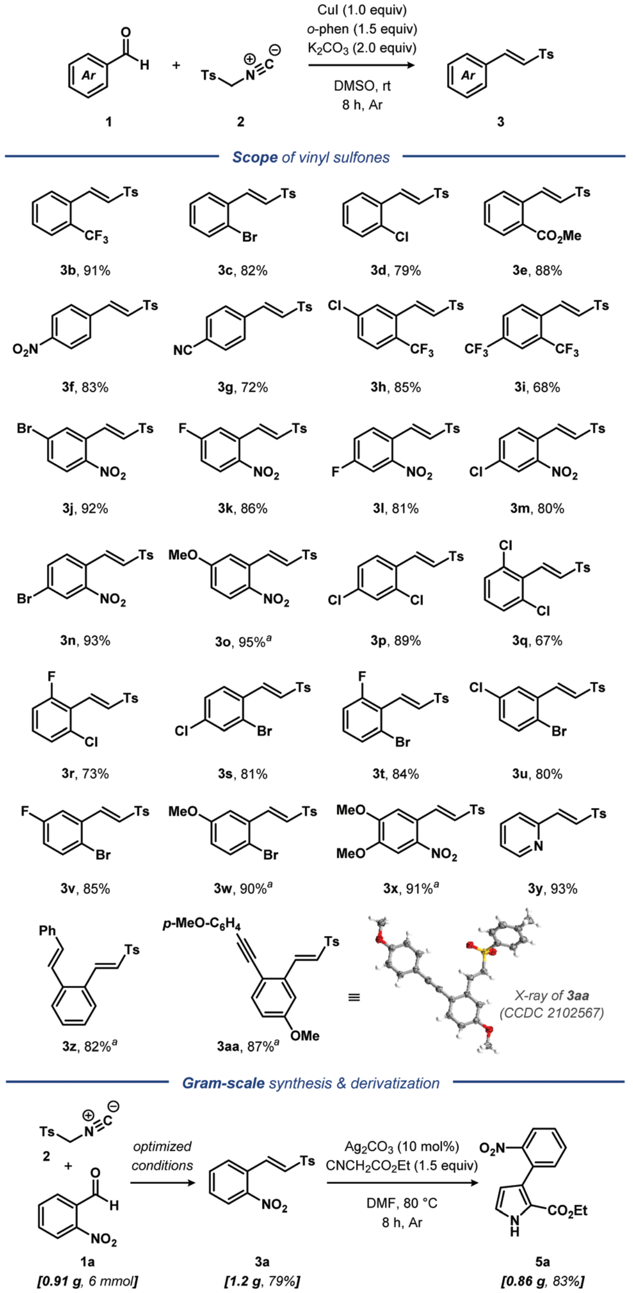
Entry	[Cu]	Base	Ligand	Solvent	Yield[b] (%) 3a	Yield[b] (%) 4a
1	—	K_2CO_3	—	DMF	0	89
2	—	Cs_2CO_3	—	DMF	0	92
3	—	DBU	—	DMF	0	73
4	CuI	K_2CO_3	—	DMF	13	83
5	$Cu(OAc)_2$	K_2CO_3	—	DMF	0	87
6	$Cu(OTf)_2$	K_2CO_3	—	DMF	0	82
7	CuCl	K_2CO_3	—	DMF	8	86
8	Cu powder	K_2CO_3	—	DMF	9	36
9	Ag_2CO_3	K_2CO_3	—	DMF	0	97
10	$Pd(OAc)_2$	K_2CO_3	—	DMF	0	84
11	CuI	K_2CO_3	*o*-Phen	DMF	21	69
12	CuI	K_2CO_3	L-Proline	DMF	16	72
13	CuI	K_2CO_3	PPh_3	DMF	14	67
14[c]	CuI	K_2CO_3	*o*-Phen	DMF	39	45
15[d]	CuI	K_2CO_3	*o*-Phen	DMF	72	24
16[e]	CuI	K_2CO_3	*o*-Phen	DMF	75	19
17[d]	**CuI**	$\mathbf{K_2CO_3}$	***o*-Phen**	**DMSO**	**88**	**<5**
18[d]	CuI	K_2CO_3	*o*-Phen	THF	63	28
19[d]	CuI	K_2CO_3	*o*-Phen	CH_3CN	54	32
20[d]	**CuI**	$\mathbf{Cs_2CO_3}$	***o*-Phen**	**DMSO**	**90**	**<5**
21[d]	CuI	DBU	*o*-Phen	DMSO	43	21

[a] Reaction conditions: **1a** (91 mg, 0.6 mmol, 1.2 equiv.), **2** (98 mg, 0.5 mmol, 1.0 equiv.), [Cu] (0.3 equiv.), base (2.0 equiv.), ligand (1.2 equiv.), solvent (2.0 mL), rt, 8 h. [b] Isolated yields. [c] 0.5 equiv. of CuI. [d] 1.0 equiv. of CuI. [e] 2.0 equiv. of CuI.

Encouraged by these results, a survey of copper salts, such as $Cu(OAc)_2$, $Cu(OTf)_2$, CuCl and copper powder, was undertaken for the reaction of **1a** and **2** in DMF at 25 °C. Here, CuI offered the highest yield of the olefinic product **3a**, while $Cu(OAc)_2$ and $Cu(OTf)_2$ were ineffective towards the formation of **3a** under the same conditions (Table 1, entries 5–8). Other transition metal-based catalysts, commonly employed in isocyanide chemistry, such as Ag_2CO_3 and $Pd(OAc)_2$, also proved ineffective (Table 1, entries 9 and 10). Delightfully, the addition of ligands slightly increased the yield of **3a** (Table 1, entries 11–13). Next, increasing the amount of the copper salt to 0.5, 1.0, and 2.0 equivalents afforded **3a** in dramatically improved yields (Table 1, entries 14 and 15). Also, the solvent had a significant influence on the transformation. Thus, changing the solvent from DMF to DMSO produced the anticipated olefinic product **3a** in up to 90% yield, while THF and CH_3CN had a negative effect on the reaction and delivered **3a** in diminished yields (Table 1, entries 17, 19 and 20). Finally, conducting the reaction with different bases identified Cs_2CO_3 as the most productive base additive (Table 1, entries 18–20). Thus, the conditions from Table 1, entries 17 and 20 were considered optimal and employed for further investigations.

With the optimized reaction conditions in hand, we explored the versatility of the developed protocol (Scheme 1). A set of diversely functionalized aromatic aldehydes **1** were reacted with TosMIC **2**, affording the corresponding olefinic products **3** in high yields (Scheme 1). The monosubstituted aromatic aldehydes **1a–1e** featuring electron-withdrawing groups on the benzene ring, such as CF_3, NO_2, Cl, Br, CO_2Me and CN, placed at either the *ortho*- or *para*-positions were compatible with the developed protocol, leading to the expected products **3a–3g** in high to excellent yields (72–91%). Similarly, a range of disubstituted substrates **1h–1w** were also efficiently transformed to the corresponding vinyl sulfones **3h–3w** in high to excellent yields (68–95%). Notably, a variety of the tolerated synthetically valuable functional groups, including fluoride, chloride and bromide, offer synthetic handles for further functionalization. Gratifyingly, the densely substituted aromatic aldehydes **1x**, **1z** and **1aa** also reacted with **2** to afford the desired products **3x**, **3z** and **3aa** in 91%, 82% and 87% yields, respectively. Notably, substrates **1z** and **1aa** containing a potentially reactive alkenyl and alkynyl group were productive under the optimized conditions, illustrating the high compatibility of the developed protocol. Furthermore, subjecting the heteroaryl substrate 2-pyridinaldehyde **1y** to **2a**, delivered the corresponding product **3y** with high efficiency. The structure of product **3w** was unequivocally confirmed by single crystal X-ray analysis (CCDC 2102567; for details, see the ESI†). Unfortunately, aliphatic aldehydes, benzaldehyde and electron-rich aromatic aldehydes including sensitive functional groups produced the corresponding oxazoles instead of the target vinyl sulfones (for additional details, see the ESI†).

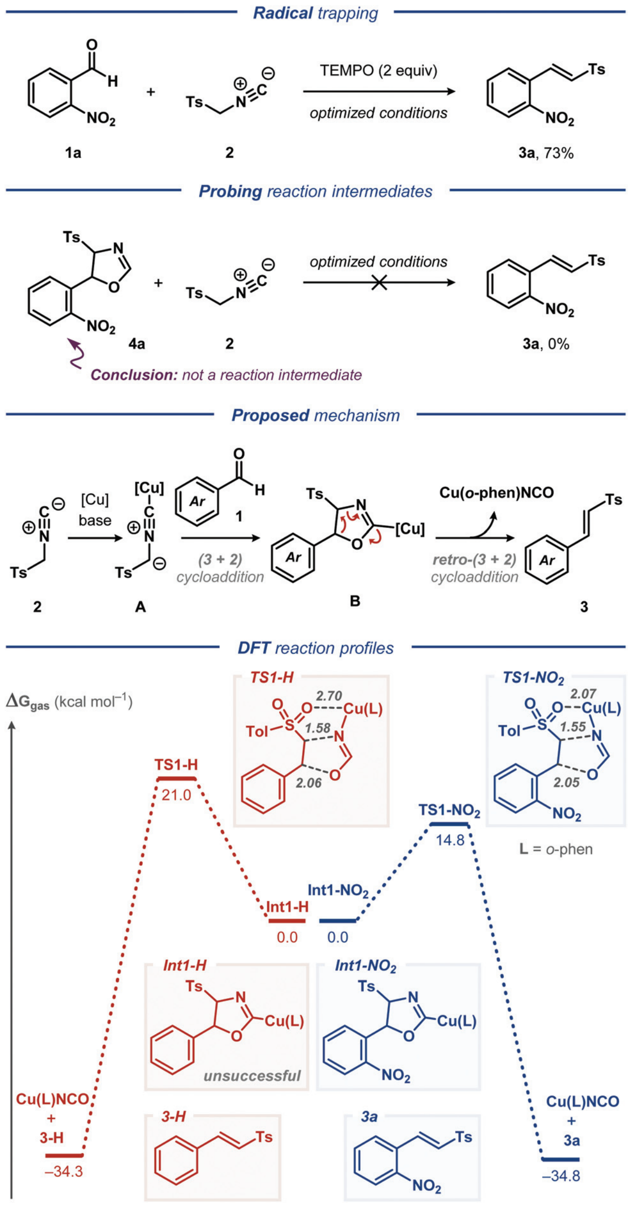
To further explore the synthetic utility and scalability of the established protocol, the reaction of 2-nitrobenzaldehyde **1a** and TosMIC **2** was carried out on a 5 mmol scale, providing the expected product **3a** in 79% yield (1.2 g). Furthermore,



Scheme 1 Substrate scope for synthesis of vinyl sulfones **3**, gram-scale synthesis and further derivatization. Reaction conditions: **1a** (0.6 mmol, 1.2 equiv.), **2** (98 mg, 0.5 mmol, 1.0 equiv.), CuI (98 mg, 0.5 mmol, 1.0 equiv.), *o*-phen (135 mg, 0.75 mmol, 1.5 equiv.), K_2CO_3 (138 mg, 1.0 mmol, 2.0 equiv.), DMSO (2.0 mL), rt, 8 h. Isolated yields. [a] 2.0 equiv. of Cs_2CO_3 instead of K_2CO_3.

vinyl sulfone **3a** was efficiently converted to oligofunctional pyrrole **5** in 83% yield through Bi's method.[13] Such oligofunctional pyrroles represent a common structural unit in numerous natural products, potent pharmaceuticals, molecular sensors, and can serve as valuable intermediates in organic synthesis.[14] Herein, we have provided a practical method for synthesis of 2,3-disubstituted pyrroles from commodity chemicals.

A series of control experiments were carried out to probe the mechanism of the established transformation (Scheme 2). First, the addition of 2 equivalents of the commonly used radical scavenger 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) to the reaction mixture did not affect the reaction and provided product **3a** in 73% isolated yield.[15] This result strongly suggests that the disclosed reaction does not proceed through a free-radical pathway. Furthermore, employing oxazole **4a** as the substrate under the optimized conditions did not produce the olefinic product **3a**, indicating that copper-activated oxazole intermediate is critical to the ring-opening step of the developed reaction.[16] Based on the experimental observations and relevant literature precedents,[17,18] a plausible mechanism



Scheme 2 Mechanistic investigations, proposed mechanism and DFT calculations. DFT reaction profiles were calculated at the B3LYP-D3(BJ)/SDD (for Cu and I)/6-31+G(d,p) (for C, H, O, N, S) level of theory.

for the formation of vinyl sulfone **3** was proposed (Scheme 2). DFT calculations were performed using the three-parameter exchange–correlation hybrid functional B3LYP[19] with D3 [20] dispersion correction for studying the possible existence of copper-activated isocyanide or copper-activated aldehyde. The results suggest that it is more reasonable for the isocyanide to preferentially coordinate to the copper center, whereas coordination of the aldehyde is not favored in this catalytic system (Fig. S1, for additional details, see the ESI†). Here, the base facilitates abstraction of the α-proton from TosMIC **2**, promoting the generation of the copper-coordinated intermediate **A**,[21] which then undergoes (3 + 2) cycloaddition to produce the annulated adduct **B** (copper-activated aldehyde). Finally, the annulated adduct **B** undergoes retro-(3 + 2) cycloaddition to give the target product **3** through the elimination of Cu(*o*-phen)NCO.[18] There may be two competing scenarios for forming copper-activated oxazole intermediates: (1) protonation or (2) elimination. Thus, the copper-activated oxazole intermediates with electron-rich aromatic rings are easily protonated to furnish oxazoles, the stability of which makes it challenging to carry out a ring-opening sequence under the optimized reaction conditions. Next, DFT calculations were performed to gain further mechanistic insight into the key ring-opening process (for details, see the ESI†). As shown in Scheme 2, the retro-(3 + 2) cycloaddition processes of **Int1-H** and 2-nitrobenzoxazole copper intermediate **Int1-NO$_2$** were explored, suggesting that **Int1-NO$_2$** is significantly more reactive than **Int1-H**. The reaction barrier for **TS1-H** is 20.9 kcal mol^{-1}, while the nitrobenzoxazole copper intermediate in **TS1-NO$_2$** has a significantly lower barrier of 14.8 kcal mol^{-1}. This contrasts the concerted cleavage of C–N and C–O bond in **TS1-H**, which in **TS1-NO$_2$** is also concomitant with the migration of copper from the carbon to the nitrogen site. Thus, we speculate that the electron-withdrawing nitro group in **Int1-NO$_2$** promotes the migration of copper and further reduces the energy barrier of the reaction.

Conclusions

In conclusion, we report a novel copper-assisted Wittig-type olefination reaction of aldehydes with TosMIC under mild reaction conditions, providing a convenient approach to an array of functionalized vinyl sulfones in good to excellent yields. Based on experimental and computational investigations, an intriguing electronically controlled (3 + 2)/retro-(3 + 2) cycloaddition sequence is proposed. Considering the importance of the Wittig reaction and the relevance of vinyl sulfones as building blocks, this methodology will undoubtedly find practical applications in the future. Further investigation into applying this catalytic system to aromatic ketones is currently underway.

Conflicts of interest

There are no conflicts to declare.

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