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Multicomponent aromatic and benzylic Mannich reactions through C–H bond activation

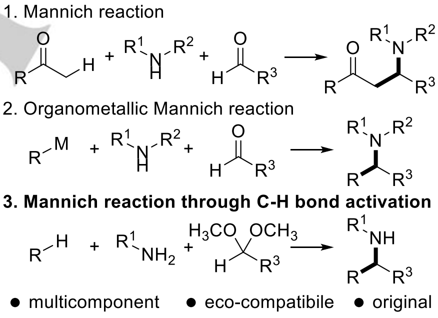
Tania Xavier,[a] Corinne Rayapin,[a] Erwan Le Gall,*[a] Marc Presset*[a]

Abstract: Multicomponent Mannich reactions through C–H bond activation is described. These transformations allowed the straightforward generation of densely substituted benzylic and homo-benzylic amines in good yields. The reaction involves a reaction between two transient species: an organometallic species, generated by transition metal-catalyzed sp^2 or sp^3 C–H bond activation and an *in situ* generated imine. The use of an acetal as an aldehyde surrogate was found essential for the reaction to proceed. The process could be successfully applied to Rh(III)-catalyzed sp^2 C–H bond functionalization and extended to Cu(II)-catalyzed sp^3 C–H bond functionalization.

Introduction

One century after its discovery,[1] the Mannich reaction has become one of the most important reactions in organic synthesis.[2] Therefore, this venerable reaction has been frequently used as a powerful and practical route to densely substituted amines, a common feature of numerous natural products or pharmaceutical compounds.[3] Such a success could definitely be linked to the intrinsic features of this transformation. Indeed, in addition to a straightforward access to nitrogen-containing scaffolds, the Mannich reaction constitutes a fundamentally powerful C–C and C–N bonds forming reaction, due to the opportunity of operating under multicomponent conditions using simple and varied starting materials.[4] Apart from the classical aminoalkylation of carbonyl compounds using enols and enolates (Scheme 1.1), recent improvements of the reaction have focused on the use of other nucleophiles such as organometallic species, thus contributing to greatly expand the usefulness of this class of reactions (Scheme 1.2).[5] Nevertheless, this strategy usually relies on the use of halides and stoichiometric amounts of metals thus producing large amounts of wastes.

A modern and greener solution to this issue is the use of C–H bond activation by transition metal complexes which proved very efficient for the functionalization of sp^2 C–H bonds.[6],[7] In the case of the addition of C–H bonds to polarized π bonds,[8] the functionalization of sp^2 C–H bonds by imines has been initially achieved by Ellman and Shi using Rh(III)-catalysis and,[9] shortly after, by Yoshikai and by Matsunaga and Kanai using Co(I) and Co(III)-catalysis, respectively.[10] However, despite the major advances provided by these contributions, only preformed imines proved to constitute suitable substrates and procedures merging C–H bond activation and multicomponent conditions remain desirable. Indeed, the field of multicomponent reactions based on C–H bond activation, which constitutes a reliable tool for straightforward access to molecular diversity, is still in its infancy.[11] In the case of Rh(III) catalysis, the rare recent examples of multicomponent reactions involved the reaction of the organometallic species generated via C–H bond activation with bench-stable reagents.[12] In continuation of our work on organometallic Mannich reactions,[13] we describe herein the development of multicomponent Mannich reactions through transition metal-catalyzed C–H bond functionalization by reaction between two transient species, an organometallic species and an imine, both being generated *in situ* (Scheme 1.3).



Scheme 1. Multicomponent Mannich reactions.

Results and Discussion

The development of the aimed reaction using arenes bearing a 2-pyridinyl directing group[14] required a deep investigation of the reaction conditions.[15] As a model reaction, we first studied the use of a 1:1 mixture of benzaldehyde **3a** and tosylamide **2a** with 2-phenylpyridine **1a** in the presence of Rh(III)-catalysis (Table 1). Disappointingly, none of the reported conditions proved to be efficient in the case of such a multicomponent protocol as only minor amounts were detected (entries 1 and 2). As mechanistic studies performed by Ellman revealed an inhibition of the reaction by **1a**,[16] we tested the use of a reversed stoichiometry and this modification allowed us to obtain a better but still limited yield of 14% (entry 3). We next evaluated the influence of the introduction of an excess of reagents on the reaction outcome in DCE, as the use of a protic solvent such as *t*-BuOH could be detrimental to the imine formation. While the addition of an excess of **2a** or **3a** had no impact, (entries 4 and 5) the addition of two equivalents of water, the side-product of imine formation,

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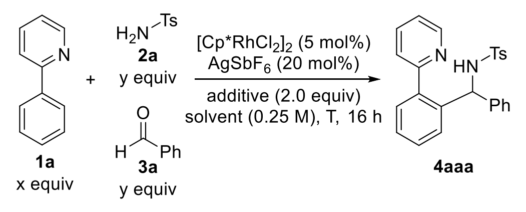
proved detrimental to the reaction (entry 6). Moreover, a rise of the temperature to 120 °C was indeed beneficial (24%) but the reaction remained limited (entry 7).

Table 1. Initial findings and limitations.[a]

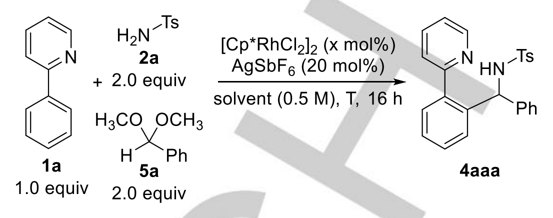


Entry	**1a**:**2a**:**3a**	Additive	Solvent	T (°C)	Yield (%)[b]
1	1:2:2	-	*t*-BuOH	90	9
2	2:1:1	-	DCE	90	traces
3	1:2:2	-	DCE	90	14
4	1:2:2	**2a**	DCE	90	14
5	1:2:2	**3a**	DCE	90	14
6	1:2:2	H_2O	DCE	90	7
7	1:2:2	-	DCE	120	24

[a] All reactions were performed on a 0.1 mmol scale in 10 mL sealed tubes. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard.

In order to avoid the presence of water in the reaction, we decided to switch from benzaldehyde **3a** to the corresponding dimethyl acetal **5a** (Table 2), as the use of water scavengers (4 Å ms or $MgSO_4$) was not beneficial to the reaction. This simple modification resulted in a significant improvement of the reaction as the desired product was thus obtained in 44% (entry 1). As the use of a higher reaction temperature (160 °C) was not beneficial (28%, entry 2), we focused on the nature of the solvent. Chlorinated solvents (entries 3-5) were efficient but their toxicity was a serious drawback.[17] We thus evaluated other classical polar protic solvents (entries 6-9) but none of them was as efficient as CCl_4. Among polar solvents, strongly coordinating ones such as CH_3CN or DMF showed no product formation but the use of THF, a moderately coordinating solvent, was highly efficient (73%, entry 10).[18] Using this solvent, the catalyst loading could be decreased to 2.5 mol% (entries 11 and 12), allowing the isolation of the expected protected diarylmethylamine **4aaa** in 80% yield. After verifying that no reaction occurred in the absence of $[Cp^*RhCl_2]_2$ or $AgSbF_6$ and by changing the silver salt to $AgNO_3$, the scope of the reaction was explored under such optimized conditions:[19] **1**:**2**:**5** = 1:2:2, $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (20 mol%), THF, 120 °C, 16 h.

Table 2. Optimization of the reaction conditions.[a]

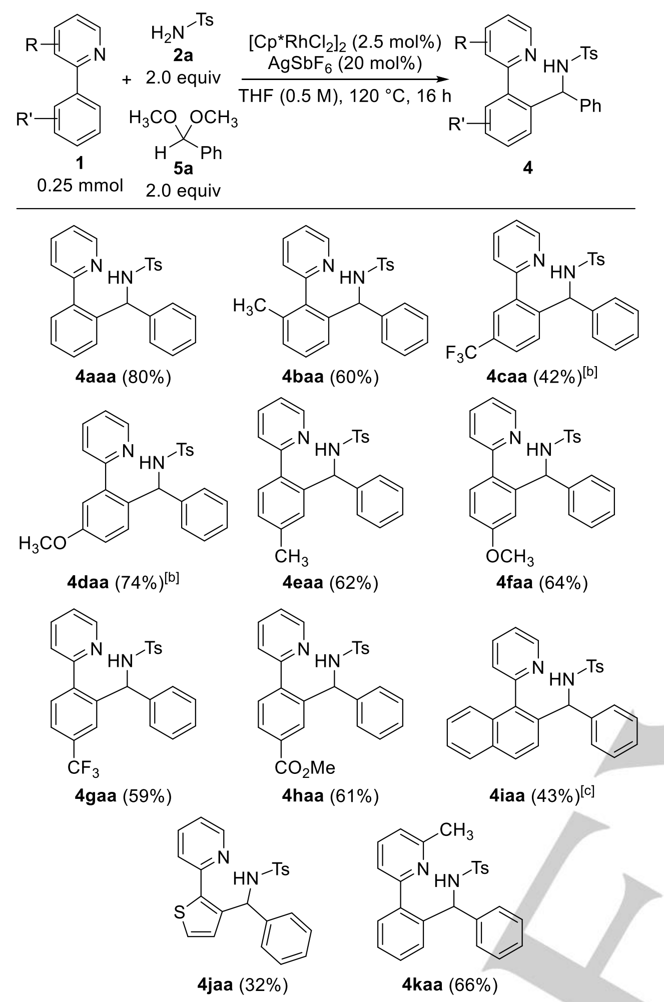


Entry	x	Solvent	T (°C)	Yield[b]
1	5	DCE	120	44
2	5	DCE	160	28
3	5	CH_2Cl_2	120	32
4	5	$CHCl_3$	120	49
5	5	CCl_4	120	72 (55)[c]
6	5	CH_3OH	120	23
7	5	TFE	120	48
8	5	*t*-BuOH	120	27
9	5	AcOH	120	10
10	5	THF	120	73[c]
11	2.5	THF	120	80[c]
12	1	THF	120	50

[a] All reactions were performed on a 0.1 mmol scale in 10 mL sealed tubes. [b] Determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. [c] Isolated yield.

This Rh(III)-catalyzed aromatic Mannich reaction tolerates a large range of each reaction partner.[20],[21] Substitution of the 2-aryl pyridine **1** is tolerated in all positions (Table 3). Introduction of a methyl group in the *ortho*-position allowed the formation of **4baa** in a correct 60% yield. When substitution is introduced in the *meta*-position, the reaction is regioselective and occurs at the less hindered C–H bond. Moreover, the use of a strong EDG afforded a much better yield **4daa** (74%) than an EWG (**4caa**, 42%), presumably by increasing the nucleophilicity of the organometallic species. This effect is much less pronounced in the case of *para*-substituted aryl pyridines and the desired product is always obtained in good yield (59-64%), regardless of the nature of the group. In the case of **1i**, the desired product is obtained in a lower yield (43%) because of a competitive C8-functionalization. Interestingly, the present conditions could also be used in the case of the thiophene derivative **1j** leading to the functionalization of the heteroaromatic ring in 32%. Substitution of the pyridine ring was briefly examined, and the introduction of a methyl group close to the nitrogen atom delivered a lower 66% yield of **4kaa**.

Table 3. Scope of 2-aryl pyridines.[a]

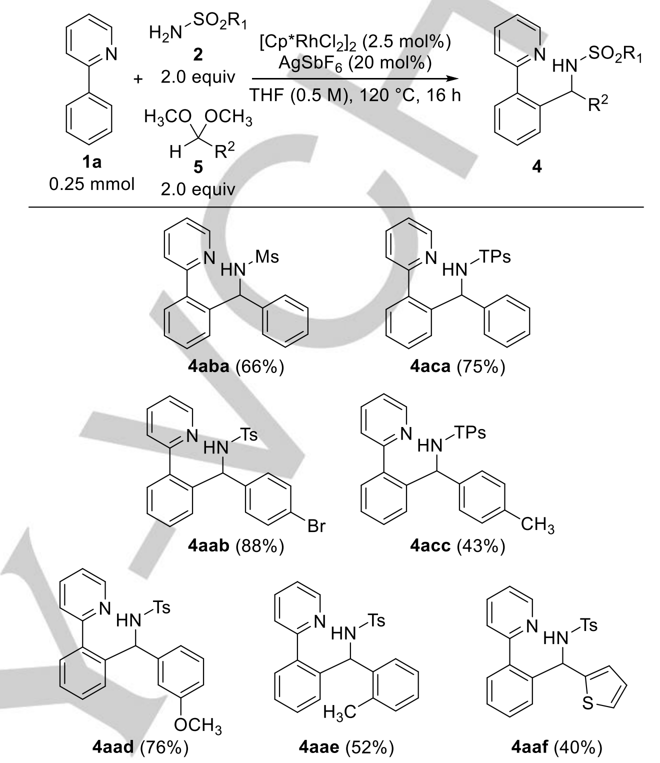


4aaa (80%) **4baa** (60%) **4caa** (42%)[b]
4daa (74%)[b] **4eaa** (62%) **4faa** (64%)
4gaa (59%) **4haa** (61%) **4iaa** (43%)[c]
4jaa (32%) **4kaa** (66%)

[a] Yields of isolated products. Reaction conditions: **1** (0.25 mmol), **2** (2.0 equiv), **5** (2.0 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (20 mol%), THF (0.25 M), 120 °C, 16 h. [b] Regioselectivity > 95:5. [c] Regioselectivity = 80:20.

A variety of sulfonyl amines **2** and acetals **5** could also be used (Table 4). Mesylamide **2b** appeared to be less efficient (66%) than tosylamide **2a**, and *tert*-butyl carbamate ($BocNH_2$) or *tert*-butanesulfinamide only led to complex mixtures. However, 2-thiophenesulfonamide **2c** delivered the expected **4aca**, bearing a 2-thiophenesulfonyl group on the nitrogen atom,[22] in a good 75%. A large range of substituents was tolerated on the aromatic ring of acetals **5**. Thus, the introduction of a bromine atom on the *para* position was well-tolerated, delivering **4aab** in a high 88% yield, whereas the introduction of a methyl group afforded **4acc** in 43%. In the case of *meta*-substituted starting materials, **5d** led to **4aad** in 76% while the isolated yield was lower with 2-methyl benzaldehyde derivative **5e**, presumably due to steric hindrance (52%). Even if the reactions performed with phenylacetaldehyde or acrolein dimethyl acetals only led to complex mixtures, the heteroaromatic derivative **5f** could be used to obtain product **4aaf** in a decent 40%.

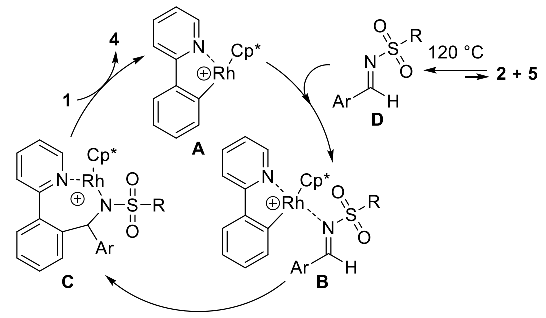
Table 4. Scope of sulfonamides and acetals.[a]



4aba (66%) **4aca** (75%)
4aab (88%) **4acc** (43%)
4aad (76%) **4aae** (52%) **4aaf** (40%)

[a] Yields of isolated products. Reaction conditions: **1** (0.25 mmol), **2** (2.0 equiv), **5** (2.0 equiv), $[Cp^*RhCl_2]_2$ (2.5 mol%), $AgSbF_6$ (20 mol%), THF (0.25 M), 120 °C, 16 h. TPs = 2-thiophenesulfonyl.

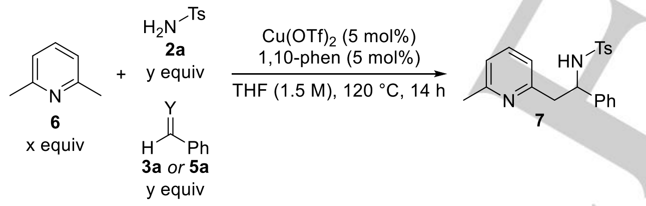
The mechanism of the present multicomponent reaction involves the *in situ* generation of a highly electrophilic imine[23] by condensation of the sulfonamide **2** with the acetal **5**, as this intermediate has been systematically detected in the reaction mixture.[24] Once being formed, the addition of the 2-arylpyridine **1** on this imine probably follows the elementary steps described by Ellman and Shi:[16] the coordination of the imine **D** with cationic rhodacycle **A** is followed by insertion of the C–N double bond into the C–Rh bond to provide **C**. Although the regeneration of the catalytic species **A** diverged in these studies, it implies the formation of **4** and the C–H bond activation of **1** (Scheme 2).



Scheme 2. Mechanism of the reaction.

As the formation of the imine is supposed to be independent of the C–H bond activation step, it was anticipated that the present approach should be applicable to other transformations, such as the multicomponent Mannich reaction through sp^3 C–H bond activation.[25] This approach being previously described by Manolikakes using a Brønsted acid catalyst,[26] we focused on the use of $Cu(OTf)_2$ as a Lewis acid catalyst. We thus investigated the reaction between 2,6-lutidine **6**, tosylamide **2a** and benzaldehyde **3a** or its dimethyl acetal **5a** in THF at 120 °C (Table 5). Even if no beneficial effect of using an excess of the imine precursors was detected (entries 1 and 2), the use of **5a** revealed superior to the use of **3a** in each case: 68% instead of 62% when using an excess of **6** (entries 3 and 4).

Table 5. Extension to sp^3 C–H bond functionalization.[a]



Entry	Reagent	x:y	Yield (%)[b]
1	**3a**	1:2.5	58%
2	**5a**	1:2.5	62%
3	**3a**	2.5:1	62%
4	**5a**	2.5:1	68%

[a] Yields of isolated products. Reaction conditions (0.3 mmol scale): **6** (x equiv), **2a** (y equiv), **3a** or **5a** (y equiv), $Cu(OTf)_2$ (5 mol%), 1,10-phenanthroline (5 mol%), THF (1.5 M), 120 °C, 14 h. [b] Isolated yields.

Conclusions

In conclusion, we have developed multicomponent Mannich reactions through transition metal-catalyzed C–H bond functionalization. This reaction allows the straightforward preparation of densely substituted amines by reaction between a C–H containing pronucleophile, a sulfonamide and an acetal. The use of this latter in overheated THF was found to be essential to overcome the detrimental release of water during imine formation and to ensure efficiency of the multicomponent approach. These conditions were successfully applied to either Rh(III)-catalyzed sp^2 C–H bond activation or Cu(II)-catalyzed sp^3 C–H bond activation, opening the way to a renewal of multicomponent Mannich reactions.

Experimental Section

General procedure: In air, an oven-dried 10 mL reaction tube equipped with a stir bar was charged with $[Cp^*RhCl_2]_2$ (3.9 mg, 6.2 µmol, 2.5 mol%), $AgSbF_6$ (17.2 mg, 0.05 mmol, 20 mol%) and sulfonamide **2** (0.5 mmol, 2.0 equiv), closed with a septum and flushed with Ar. THF (0.5 mL, C = 0.5 M), 2-aryl pyridine **1** (0.25 mmol, 1.0 equiv) and aryl aldehyde dimethyl acetal **5** (0.5 mmol, 2.0 equiv) were successively added and the tube was sealed with a screw stopper. The reaction was stirred at 120 °C (external temperature) for 16 h. Then, the reaction mixture was filtered through a plug of Celite (thoroughly rinsed with EtOAc) and the filtrate was evaporated. The crude material was purified by FC to afford the desired product **4**.

Acknowledgements

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Keywords: Multicomponent reactions • C–H activation • Mannich reactions • Synthetic methods

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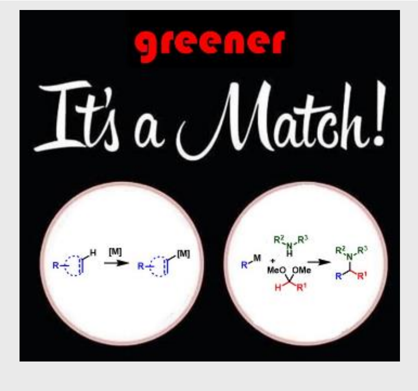

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