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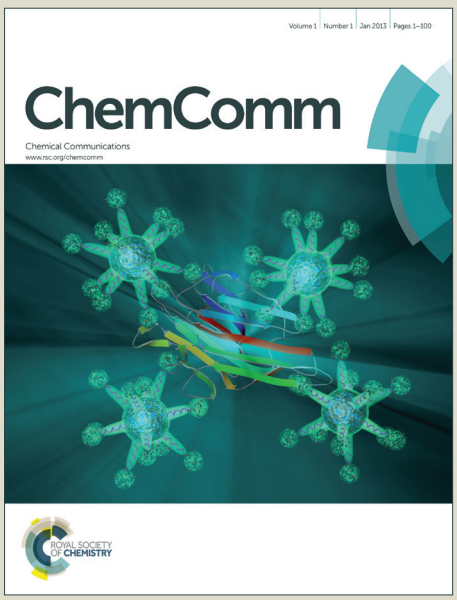

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Highly efficient dual catalysis approach for *C*-glycosylation: addition of (*o*-azaaryl)carboxaldehyde to glycals

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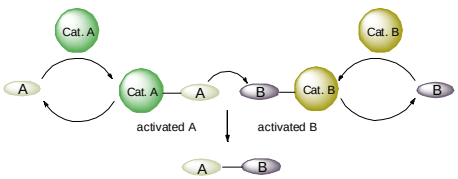
A novel and efficient dual catalysis approach by concurrent activation of glycals and (*o*-azaaryl)-carboxaldehydes using palladium and N-heterocyclic carbene has been developed. The two electrophiles could react after activation through formation of Breslow intermediate and *π-allyl* Pd complex, widening the scope of reacting glycosylation partners and opening up possibilities for future glycosylation.

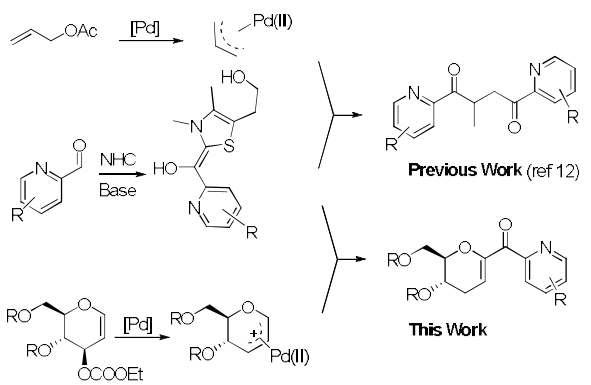
Dual catalysis is an emerging field in catalytic chemistry, which has attracted increasing attention because of its promising potential extension to many seemingly unreactive reactants, through concurrent activation of electrophile and nucleophile (Figure 1).[1] Despite the useful application of dual catalysis, it is still uncommonly explored due to the prerequisite of having two catalysts that are compatible under the reaction conditions.[2] In particular, the organo catalyst-metal combination for cooperative dual catalysis has attracted much interest. So far, the most commonly used electrophiles are the cationic organometallic complexes activated by transition metal catalysts such as palladium[3], ruthenium[4], and iridium[5] while nucleophiles include vanadium-allenoates[3b], enamines[3a, 3c, 3d, 3f, 3g, 4a,5] and enones.[3e]

Figure 1 Cooperative catalysis through dual activation



The translation of dual catalysis to carbohydrate chemistry would be an important advancement to current glycosylation methods by allowing a wider range of substrates to react with glycals upon activation. Our synthetic methodology would be especially significant because of the importance of *C*-glycoside products,[6] due to their activity in enzymatic and metabolic chemistry,[7] frequent occurrence in natural products[8] and potential to serve as chiral building blocks in synthetic chemistry[9].

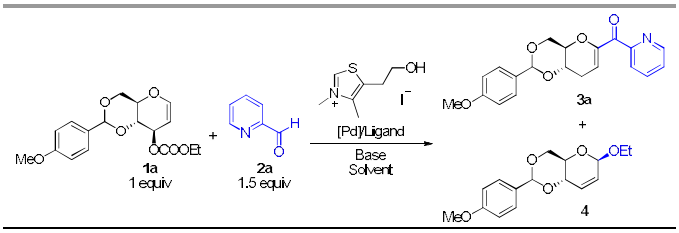
Figure 2 Dual catalysis of allylic system and Breslow intermediate



Our strategy is to combine the two seemingly unreactive electrophilic reactants, aldehydes and glycals, to form *C*-glycosides. This would be made possible by the N-heterocyclic carbene catalyzed umpolung of aldehyde to form Breslow intermediate to attack the electrophilic π-allyl Pd complex.[10] However, the challenge is the selective attack of π-allyl Pd complex instead of aldehyde

starting material upon the umpolung activation. This is particularly so as the resulting Pd-glycal complexes[11] are substantially electrophilic and are reported to be able to react with a variety of nucleophiles, such as enolates[11a], imidazoles[11b], alcohols and phenols[11c]. Encouraged by our recent discovery[12], we envisaged that the dual catalyzed *C*-glycosylation reactions of glycals and (*o*-azaaryl)carboxaldehydes (Figure 2) could proceed, driven by the faster reaction rate and higher affinity between the two activated species than the activated species with reactant.

Table 1 Condition optimization [a]

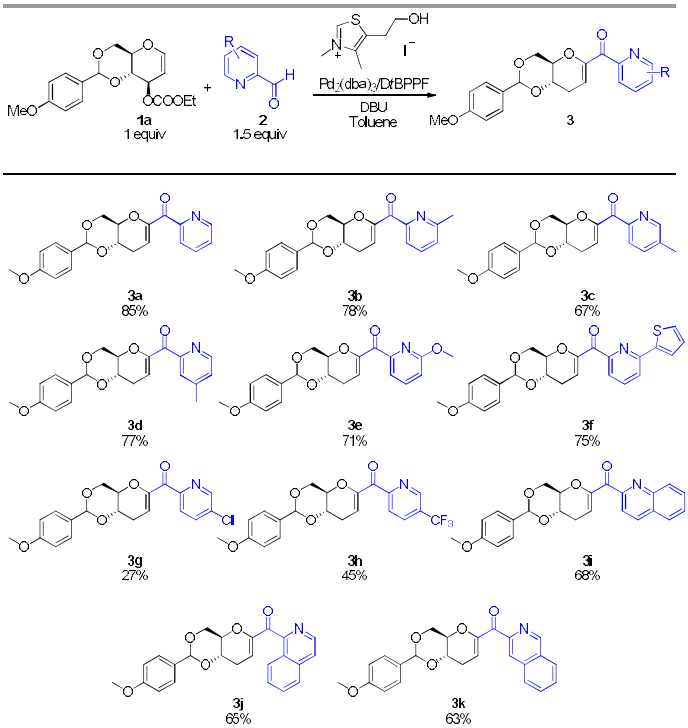


Entry	Pd source	Ligand	Base	Solvent	T (^{o}C)	Yield **3a** (**4**)[b](%)
1	$Pd(PPh_3)_4$	—	NEt_3	DCM	50	0 (0)
2	$Pd(PPh_3)_4$	DPPB	NEt_3	DCM	50	20 (22)
3	$Pd(OAc)_2$	DPPB	NEt_3	DCM	50	trace (25)
4	$Pd(TFA)_2$	DPPB	NEt_3	DCM	50	0 (<5)
5	$Pd(PPh_3)_4$	D*i*PPF	NEt_3	DCM	50	35 (50)
6	$Pd_2(dba)_3$	D*i*PPF	NEt_3	DCM	50	45 (38)
7	$Pd(dba)_2$	D*i*PPF	NEt_3	DCM	50	24 (45)
8	$Pd_2(dba)_3$	D*t*BPF	NEt_3	DCM	50	57 (23)
9	$Pd_2(dba)_3$	D*t*BPF	NEt_3	Toluene	80	71 (10)
10	$Pd_2(dba)_3$	D*t*BPF	DBU	Toluene	80	85 (<5)
11	$Pd_2(dba)_3$	D*t*BPF	Cs_2CO_3	Toluene	80	40 (15)
12	$Pd_2(dba)_3$	D*t*BPF	K_2CO_3	Toluene	80	62 (12)
13[c]	$Pd_2(dba)_3$	D*t*BPF	DBU	Toluene	80	75 (<5)

[a] Unless otherwise specified, reactions were carried out with 1.5 equivalent aldehyde, 1 equivalent base, 10 mol% Pd catalyst, 15 mol% ligand, 20 mol% NHC. [b] Isolated yield. [c] This reaction was carried out with 2.5 mol% $Pd_2(dba)_3$ and 7.5 mol% D*t*BPF. DPPB: 1,4-bis(diphenylphosphino)butane, D*i*PPF: 1,1'-bis-(diisopropyl-phosphino)-ferrocene, D*t*BPF: 1,1'-bis(ditertbutylphosphino)-ferrocene.

Our initial effort began with the coupling of 3-(ethoxycarbonyloxy)-4,6-*para*-methoxybenzylidene-D-glucal **1a** and pyridine-2-carboxaldehyde **2a** in the presence of $Pd(PPh_3)_4$, 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide and triethylamine in DCM under 50 ^{o}C (Table 1, entry1). No new compound was observed after 48 hours. Upon addition of DPPB ligand while keeping the other conditions constant, we managed to obtain the desired *C*-glycoside **3a** in 20% yield (Table 1, entry 2). However, the corresponding *O*-glycoside **4** was also isolated in 22% yield since the nucleophilic ethanol was generated during the decarboxylative step. Delighted with this finding, we went on to screen other commonly used palladium catalysts. The results showed that Pd(II) catalysts such as palladium acetate (Table 1, entry 3) and palladium trifluoroacetate (Table 1, entry 4) barely gave any desired product. On the other hand, attempts by using Pd(0) catalysts with a better ligand D*i*PPF (Table 1, entry 5-8) revealed that $Pd_2(dba)_3$ was the best Pd source. Further screening of ligands showed that D*t*BPF (Table 1, entry 8) was able to give a higher yield. The use of toluene as solvent and increase of temperature to 80 ^{o}C (Table 1, entry 9) gave more than 70% yield. Screening of bases commonly used in NHC catalyzed reactions (Table 1, entry 10-12) indicated that DBU was the most suitable base for this coupling reaction. When the loading of the Pd catalyst and the ligand was decreased, the yield was greatly affected (Table 1, entry 13).

Table 2 Substrate scope of aldehydes [a, b]

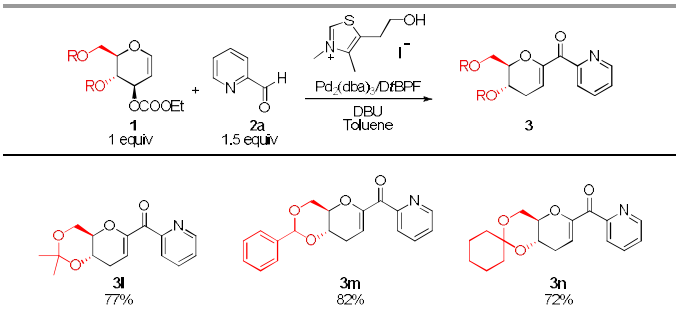


[a] Reactions were carried out with 1.5 equivalent aldehyde, 1 equivalent DBU, 5 mol% $Pd_2(dba)_3$ catalyst, 15 mol% D*t*BPF, 20 mol% NHC. [b] Isolated yield.

After obtaining the optimized reaction conditions, we proceeded to explore the substrate scope for both (*o*-azaaryl)carboxaldehydes and glycals. The substrate scope of aldehydes was summarized in Table 2. The structure of the *C*-glycoside **3a** was confirmed by X-ray crystallography.[13] A group of methyl substituted pyridine-2-carboxaldehydes were first tested. It was observed that the methyl substituents on 4, 5 and 6 positions could afford the desired products in good yields (**3b**, **3c**, **3d**) but this was not the case when 3-methyl-2-pyridine carboxaldehyde was used.[14] 2-pyridine carboxaldehydes with electron-donating groups such as methoxyl (**3e**) and thiophenyl (**3f**) also generally provided the products in good yields. In contrast, aldehydes with electron-withdrawing groups such as chloro (**3g**) and trifluoromethyl (**3h**) only gave poor to moderate yields. Besides pyridine-2-carboxaldehydes, other *o*-azaaryl-carboxaldehyde were also synthesized and examined. It was found that quinoline-2-carboxaldehyde (**3i**), isoquinoline-1-carboxaldehyde (**3j**) and isoquinoline-3-carboxaldehyde (**3k**) gave the corresponding *C*-glycosides in slightly lower yields than 2-pyridine-carboxaldehyde, which could be attributed to greater steric hindrance.

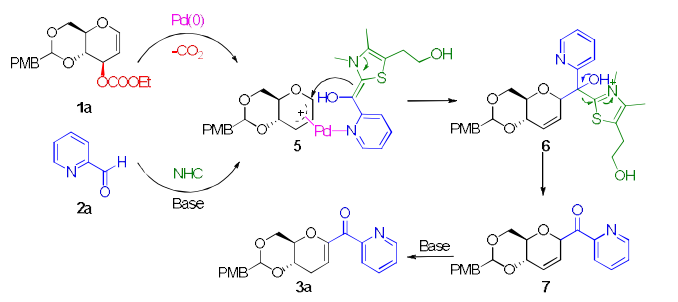
Several 3-ethoxycarbonyloxy glucals with different 4,6-protecting groups were then treated with 2-pyridine carboxaldehyde under standard condition (Table 3). The results showed that the acetal protecting groups such as isopropylidene (**3l**) benzylidene (**3m**) and cyclohexylidene (**3n**) could afford the desired *C*-glycosides in good to excellent yields.

Table 3 Substrate scope of glycals [a, b]



[a] Reactions were carried out with 1.5 equivalent aldehyde, 1 equivalent DBU, 5 mol% $Pd_2(dba)_3$ catalyst, 15 mol% D*t*BPF, 20 mol% NHC. [b] Isolated yield.

Scheme 1 Plausible mechanism



The plausible mechanism was proposed in Scheme 1. The formation of nucleophilic Breslow intermediate and electrophilic *π-allyl* Pd complex was catalyzed by NHC and Pd(0) catalysts respectively. These intermediates were brought to close spatial proximity by N-Pd coordination to form intermediate **5**. An intramolecular nucleophilic addition then took place between the allylic system and the NHC activated aldehyde part to form intermediate **6**. After the regeneration of NHC catalyst, *C*-glycoside **7** was released and proton transfer under basic condition yielded the final product **3a.**

In summary, a novel dual catalyzed *C*-glycosylation method of glycals and (*o*-azaaryl)carboxaldehydes has been developed. The substrate scope included various types of (*o*-azaaryl)carboxaldehyde and glycals with different protecting groups. This efficient approach for *C*-glycosylation would expand the range of coupling partners for glycosylation and allow useful and diverse functionalization on glycals for further transformation. Exploration of potential biological activity and further functionalization of the product is currently undergoing in our laboratory.

Notes and references

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†Electronic Supplementary Information (ESI) available: General experimental procedures and spectral charts of all products. See DOI: 10.1039/b000000x/

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