# Protecting group-free and 1,2-*trans*-selective glycosylation of carboxylic acids

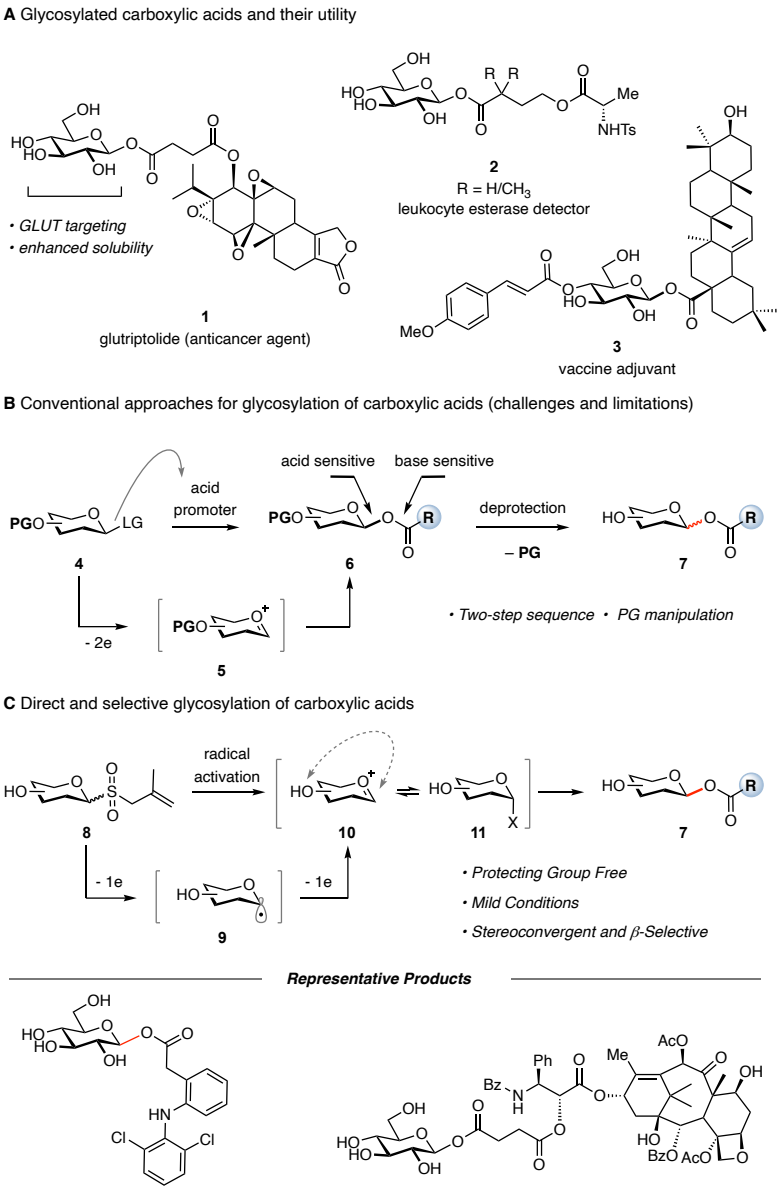
Hao Zuo, Chen Zhang, Dawen Niu

**Affiliations:**

[1]State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, and School of Chemical Engineering, Sichuan University, Chengdu, China.

*Correspondence to: niudawen@scu.edu.cn

**Abstract:** Here we report a simple and general method to achieve fully unprotected, 1,2-*trans*- (β-) selective glycosylation of carboxylic acids employing allyl glycosyl sulfones as donors. This reaction occurs under ambient temperature and basic conditions under visible light irradiation. The method is stereoconvergent, as allyl glycosyl sulfone donors pass through glycosyl radical intermediates, en route to glycosyl electrophiles. Thanks to the unique radical-based donor activation mechanism, fully unprotected glycosyl donors can be used directly. This transformation displays remarkable substrate scope with respect to both reaction partners. To illustrate its generality and potential utility, a number of commercial drugs and an acid derived from anticancer agent paclitaxel were efficiently glycosylated. Experimental and theoretical studies provide insights into the origin of the stereochemical outcome of this reaction.




**Scheme 1. Glycosylation of Carboxylic Acids: Utility and Methods.**

Glycosylation is a ubiquitous process in Nature, which modulates the trafficking, physical properties and bioactivities of various biomolecules.[1-2] Such a strategy is often emulated in the field of drug development.[3-4] The installation of carbohydrate moieties would endow target molecules with improved water solubility, tissue selectivity, and sometimes metabolic stability. Therefore, the development of simple and straightforward glycosylation methods represents a highly desirable goal in synthesis.[5-6] However, it remains a significant challenge to accomplish, due to the structural complexity of sugar donors. The task becomes more demanding when the target to be glycosylated is structurally complicated as well. Simple, selective, and functional group tolerant glycosylation methods are to be developed to address the above challenge.

Carboxylic acid is among the most frequently encountered functional groups in chemistry. A significant number of commercial drugs contain carboxylic acid groups, including blockbuster drugs ibuprofen and

indomethacin.[7] Glycosylation on carboxylic acid groups is a frequently adopted strategy in drug discovery endeavors. Due to the readily cleavable ester group in the resulting products, glycosylated carboxylic acids usually release carbohydrates and the parent carboxylic acids in body. For example, upon installation of a glucosyl group, the anticancer agent triptolide becomes more water soluble and more tumor selective (see **1** in Scheme 1). [8-9]Amino acid derivative **2** was designed as a probe for detecting leucocyte esterase as a signal of infection.[10] Triterpene derivative **3** is used as a vaccine adjuvant. Besides, glycosylated carboxylic acids are frequently encountered in natural products as well.[11]

In chemistry, the glycosylation of carboxylic acids represents a rather nontrivial task. The challenges stem from the following reasons. First, as depicted in Scheme 1a, a typical glycosylation reaction commences with the activation of glycosyl donor to form an electrophilic intermediate, which is then trapped by a nucleophile (here a carboxylic acid) to give the desired product.[12] As in most of the currently developed glycosylation methods, the use of protecting group on glycosyl donors is required to avoid interference of free hydroxyl groups with the activation stage and/or trapping stage of the process. However, the removal of protecting groups could become very difficult due to the fragile nature of ester groups in **7**. Thus, the choice of protecting groups is limited if fully unprotected products # are to be prepared. In addition, the above drawback also renders the preparation of stereo-defined glycosylated acids difficult, because the control of stereoselectivity during formation of glycosidic bonds is often reliant on the use of proper protecting groups. Recently, Takeo Kawabata reported the use of Mitsunobu glycosylation to deliver unprotected glycosylated carboxylic acids. However, such reaction requires access and handling of stereochemically pure but highly epimerizable hemiacetal starting materials.[13]

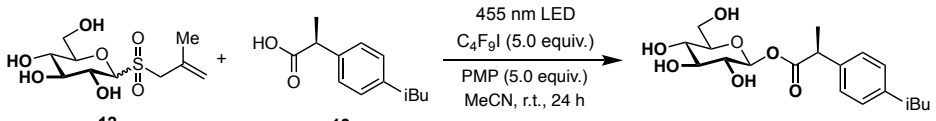
Our group has been interested in the development of simple, general and stereoselective glycosylation reactions. [14-15]We have recently reported an *O*-glycosylation method that proceeds by radical activation of glycosyl donors. Instead of using acidic promoters, we harnessed radical species to initiate a cascade which converts bench-stable allyl glycosyl sulfones to electrophilic intermediates—glycosyl iodides. The unique pathway allowed the reaction to be performed under mildly basic conditions. However, donors with benzyl protecting groups need to be employed. We reason the removal of benzyl group could be cumbersome and lower the overall reaction efficiency. Moreover, due to the hydrogen-bonding between the C2-OBn group on the donors with OH group on the acceptors, 1,2-*cis*-O-glycosides are produced predominantly. We wondered if we could employ the radical-based donor activation strategy to achieve 1,2-*trans* glycosylation of carboxylic acids, in a protecting group free manner.

In building glycosidic bonds, the 2-acyloxyl group are highly 1,2-*trans* directing.[16-17] We planned to circumvent using such a directing group since the deprotection of acyl group may become problematic. We wondered whether we could use fully unprotected glycosyl donor for glycosylation of carboxylic acids. We posit that the C2-OH group may be an effective 1,2-*trans* directing group, by forming an epoxide ring with the anomeric carbon. If realized, this method would totally obviate protecting group removal on the fragile targets, and therefore render the process more general toward a broader range of carboxylic acids and glycosyl units. Nevertheless, many potential pitfalls exist in this design. First and foremost, the use of fully unprotected glycosyl donor in building *O*-glycosidic bonds has been extremely rare. The hypothetical intermediate contains both free hydroxyl groups and an electrophilic center, and thus may undergo decomposition by polymerization. Second, little is known about the reactivities of

unprotected glycosyl donors. It is uncertain if they are long-lived enough to be trapped intermolecularly by carboxylic acids. Third, for the selective formation of 1,2-*trans*-configured products, conditions need to be identified to allow effective epoxide formation. These challenges notwithstanding, we report here the successful development of such a transformation. Our method displays significant functional group tolerance and can be used in the direct modification of many complex carboxylic acids and commercial drugs, including the anticancer agent paclitaxel.

We commenced our study using unprotected glycosyl donor **12** and (S)-(+)-Ibuprofen **13** as the model substrates (Table 1). After extensive optimization, we found that, when irradiated with a 10W 455nm blue light-emitting diode (LED) bulb, **12** reacted with **13** in the presence of $C_4F_9I$ as an initiator, PMP as a base, and MeCN as a solvent to afford the 1,2-transglycosylated product **14** in excellent yield and superior diastereomeric ratios (entry 1). Control experiments revealed some crucial factors for the reaction performance. Without $C_4F_9I$，PMP, no desired product was detected (entries 2-3). The reaction can still proceed under the condition of removing the light source, but only lower target products can be obtained (entry 4). This reaction proceeds favorably without using a representative photocatalyst (entry 1). Addition of *fac*-$Ir(ppy)_3$ as photocatalyst did not diminish the reaction efficiency (entry 5). Among various organic and inorganic bases that have been screened, PMP was the most effective (entries 6–10). This reaction could proceed in other solvents like MTBE and 1,4-dioxane, although the unprotected donor **12** with multiple hydroxyl groups has poor solubility in these solvents (entries 11-12). Especially, in the presence of solvent amounts of alcohol, this reaction could remain proceed and afford product **14** in moderate yield (entry 13). The addition of TEMPO inhibited this reaction completely (entry 14).

## Table 1. Condition Optimization.

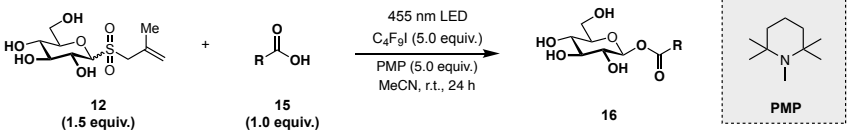



**12** (1.5 equiv.) **13** (1.0 equiv.) **14**

| Entry | Deviation from "standard conditions" | Yield (%) | β:α |
|---|---|---|---|
| **1** | **None** | **89%** | **>10:1** |
| 2 | without $C_4F_9I$ | N.R. | N.D. |
| 3 | without PMP | N.R. | N.D. |
| 4 | without light | 28% | >10:1 |
| 5 | 0.02 equiv. *fac*-Ir(ppy)$_3$ was added | 88% | 9:1 |
| 6 | $(NH_4)_2HPO_4$ instead of PMP | 6% | N.D. |
| 7 | $K_3PO_4$ instead of PMP | 44% | >10:1 |
| 8 | HTMP instead of PMP | 33% | >10:1 |
| 9 | $Et_3N$ instead of PMP | 60% | >10:1 |
| 10 | 2,4,6-collidine instead of PMP | 41% | >10:1 |
| 11 | MTBE as solvent | 51% | >10:1 |
| 12 | 1,4-dioxane as solvent | 72% | >10:1 |
| 13 | iPrOH as solvent | 61% | >10:1 |
| 14 | 1.0 equiv. TEMPO was added | N.R. | N.D. |

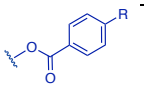
[a]Reactions in this tanle wereperformed under a $N_2$ atmosphere at 0.05 mmol scale, using 1 equiv of 16. [b]Yields are determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. [c]Diastereomeric ratios were determined by nMR analysis of the crude reaction mixture. PMP, Pempidine. N.R., no reaction; N.D., not determined.

## Scheme 2. Substrate Scope on Carboxylic Acids.

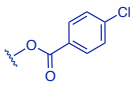



**12** (1.5 equiv.) + **15** (1.0 equiv.) → **16**

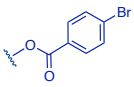
### Scope of Carboxylic Acid



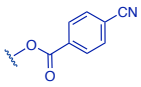
| | R | Yield | β:α |
|---|---|---|---|
| **16a** | H | 84% | > 9:1 |
| **16b** | Me | 72% | > 9:1 |
| **16c** | OMe | 63% | > 6:1 |
| **16d** | 3,5-2OMe | 57% | > 10:1 |
| **16e** | COOMe | 74% | > 5:1 |



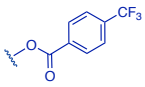
**16f,** 74%
β:α=9:1



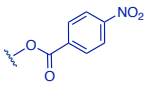
**16g,** 71%
β:α>9:1



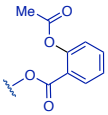
**16h,** 58%
β:α=10:1



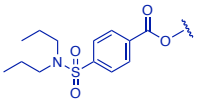
**16i,** 55%
β:α>10:1



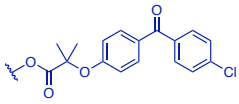
**16j,** 25%
β:α>10:1



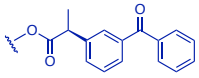
Aspirin
**16k,** 43%
β:α>10:1



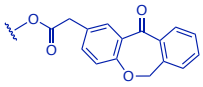
Probenecid
**16l,** 77%
β:α>9:1



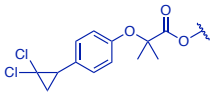
Fenofibirc acid
**16m,** 75%
β:α>10:1



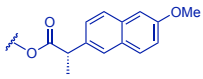
S-(+)-Ketoprofen
**16n,** 74%
β:α>10:1



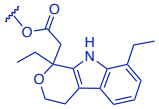
Isoxepac
**16o,** 38%
β:α>10:1



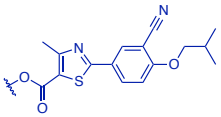
Ciprofibrate
**16p,** 84%
β:α>10:1



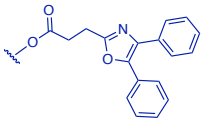
Naproxen
**16q,** 86%
β:α>10:1



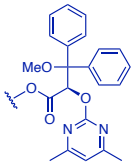
Etodolac
**16r,** 72%
β:α>10:1



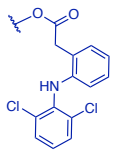
Febuxostat
**16s,** 85%
β:α>10:1



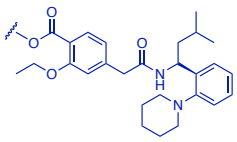
Oxaprozin
**16t,** 79%
β:α>9:1



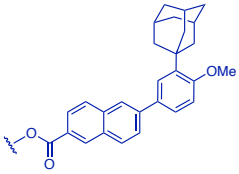
Ambrisentan
**16u,** 82%
β:α>10:1



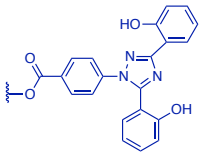
Diclofenac
**16v,** 49%
β:α>10:1



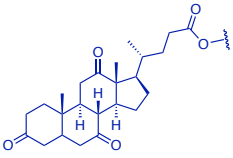
Repaglinide
**16w,** 86%
β:α>10:1



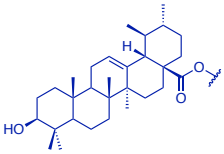
Adapalene
**16x,** 62%
β:α>10:1



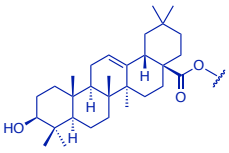
Deferasirox
**16y,** 58%
β:α>10:1



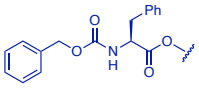
Deehydrocholic acid
**16z,** 53%
β:α>10:1



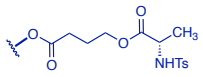
Ursolic acid
**16aa,** 67%
β:α>8:1



Oleanolic acid
**16ab,** 63%
β:α>8:1



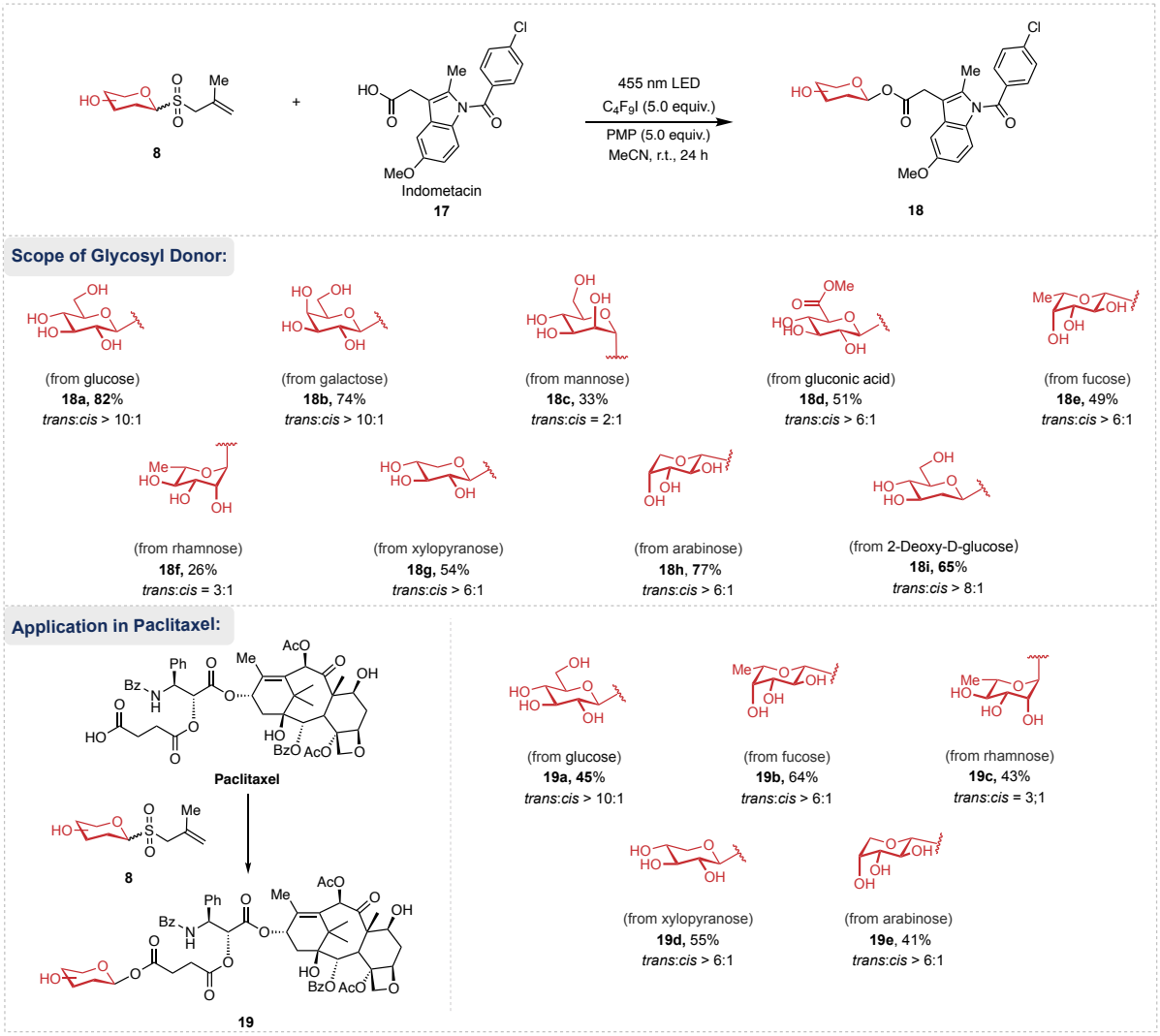
**16ac,** 87%
β:α>10:1



**16ad,** 46%
β:α>10:1

With optimal reaction conditions established, we proceeded to explore the scope of this transformation. A broad array of carboxylic acid could be glycosylated with high stereoselectivities in this reaction (Scheme 2). For example，the electron-rich (**16b-d)** and electron-deficient **(16e, 16h-j)** benzoic acids were found to be suitable substrates. Halogen substituent on aromatic rings **(16f-g, 16n, 16u)** or general alkanes **(16q)** were tolerated. Importantly, protic hydrogen atoms, such as those in free hydroxyls **(16d-e,16aa-ac, 16ae)** and secondary amides **(16s, 16w-x,16ad-ae)** which belong to the carboxylic acid were compatible with the reaction. We applied this method in the glycosylation of bioactive natural products and commercial drugs, including well-liked medications Aspirin**(16k)** and Diclofenac **(16v)**. From these examples, it is worth noting that: 1) this reaction is not only suitable for common alkyl carboxylic acid and benzoic acid derivatives, but also compatible with carboxylic acids containing heterocycles including thiazole **(16s)**, indole **(16r)**, pyrimidine **(16u)**, oxazole **(16t)**, triazole **(16y)**, 2) hindered nucleophiles such as antihypertensive drugs ambrisentan **(16u)** could also be glycosylated in good yields, 3) for drugs with poor solubility in acetonitrile such as dehydrocholic acid **(16z)** and adapalene **(16x)** and natural products with antitumor activity including ursolic acid **(16aa)** and oleanolic acid **(16ab)**, we could make these compounds glycosylated in high yield using mixed solvents (MeCN: DCM=3:1), 4) amino acids and their derivatives could be glycosylated by our method with high selectivity, as exemplified by the efficient preparation of **16ac** and **16ad.** Among them, product **16ad** has the potential to be used in glucose strips to the quantification of the severity of urinary tract and periprosthetic joint infections.

**Scheme 3. Substrate Scope on Glycosyl Donors.**



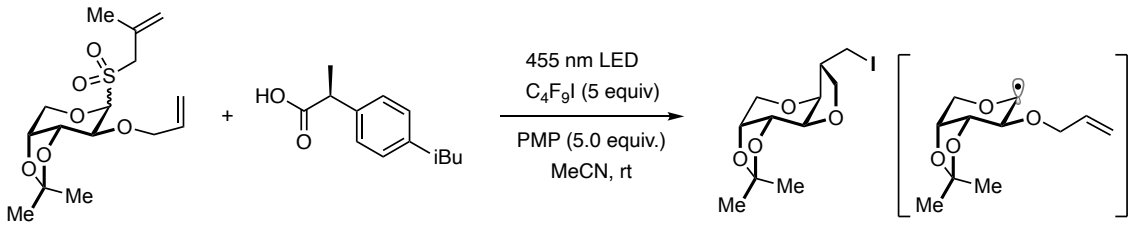

We next examined the generality of this method with respect to the glycosyl donors **(Scheme 3)**. We extended the substrate using different glycosyl donors with non-steroidal anti-inflammatory drug Indomethacin **(17)** as a substrate. We found that the unprotected glycosyl donors derived from glucose, galactose and gluconate underwent conversion into the corresponding 1,2-trans configured products with moderate yields and high selectivities **(18a-b，18d)**. Our method could be tolerated in the stereoselective preparation of 1,2-trans-pentopyranosides, which include fucopyranoside **(18e)**，xylopyranosides **(18h)** , arabinopyranosides **(18i)** and 2-deoxy-O-glucoranside **(18j)**. For mannose and rhamnose, we could only obtain 1,2-trans products with low yields and selectivity **(18c, 18f)**, which we believe may be due to the unfavorable position of the hydroxyl group in the axial position, hindering the generation of the epoxide intermediate.

To demonstrate the broad scope and utility of this method, we applied this reaction in the derivatization of Taxol using different identity of glycosyl donors (Table 3). Taxol, as a natural diterpenoid, is one of the most famous and crucial antitumor drugs in recent decades due to its excellent antitumor activity.[18-19]Yet the low water solubility of this molecule remains an obstacle for clinical use. Installing a sugar moiety onto Taxol has been examined as a

strategy to improve its water solubility. However, because of the challenge associated with the transformation, the previous studies employed non-natural glycosyl units in their studies. We attempted using perfluoro butyl iodide and unprotected allyl sulfone donors to achieve glycosylation of Taxol and improve its water solubility. We found that the unprotected glycosyl donors including glucose, fucose, rhamnose, xylose, arabinose conversion into the corresponding 1,2-trans configured products with moderate yields and selectivity **(19a-e)**. The improved water solubility and retained activity of Taxol products after glycosylation modification have been demonstrated in preliminary biological studies.[20]

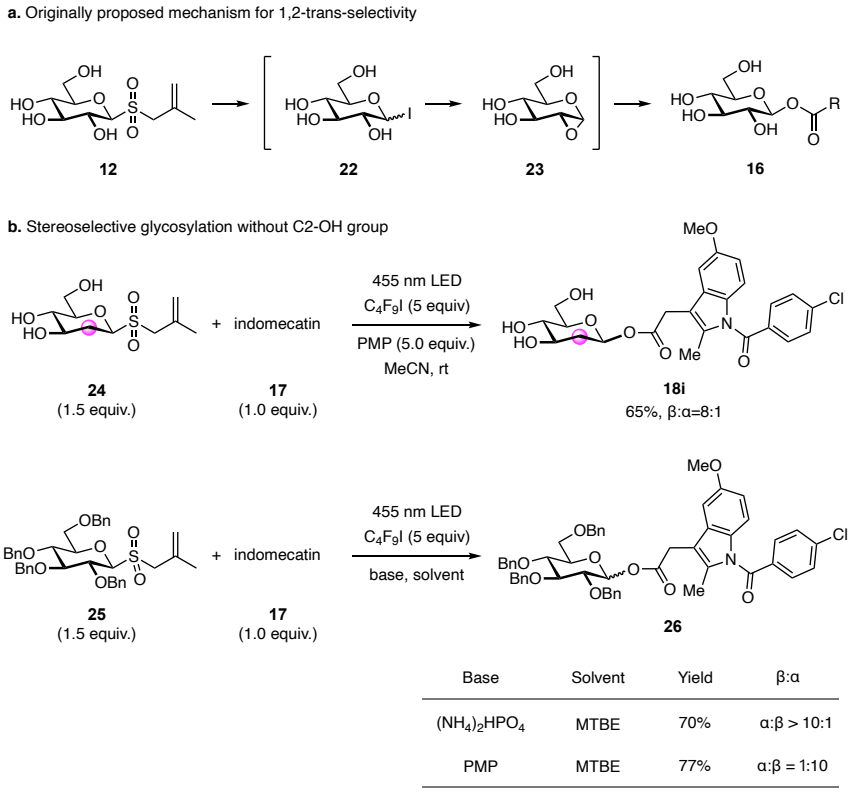
We performed experiments to understand the reaction pathway. We first prepared 2-allyloxyl substituted sulfone **20** and subjected it to our standard reaction conditions, with ibuprofen used as the acceptor. We found the bicyclic iodide **21** was formed in excellent yield, suggesting the reaction proceeds by radical intermediate **TS-I**.

**Scheme 4. Radical Clock Experiment.**




The origin of stereoselectivity outcome of this reaction was intriguing. We originally thought that the C2-OH group in the unprotected donor may be a participating group, which readily forms epoxide intermediates from the nascent glycosyl iodide (or other oxocarbenium equivalents). Subsequent attack of acceptor affords 1,2-*trans* configured products. We then performed control experiments using 2-deoxy donor **24** that does not contain a C2-OH group. To our surprise, the β-configured glycoside was formed in high selectivity as well. This result contradicts the notion that equatorially configured glycosyl halides are more reactive than the axially configured ones. We further performed the reaction using per-benzylated donor **25**. In this case, we noted that identity of base employed in this reaction plays a crucial role in determining the stereoselectivity. The 1,2-*cis* product dominated when $(NH_4)_2HPO_4$ was used, whereas the 1,2-*cis* product formed preferentially when PMP used instead. The above results suggest the nature of nucleophile could be another determining factor for stereoselectivity.

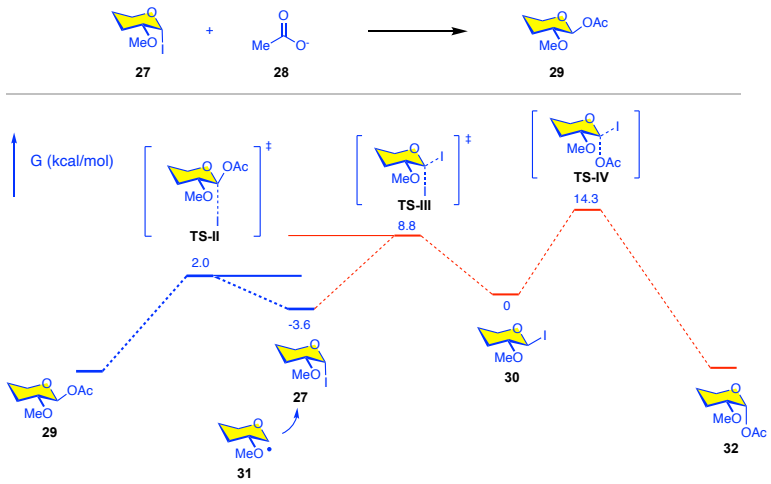
## Scheme 5. Effects of C2-substituents and Reaction Conditions on Stereochemical Outcomes.




| Base | Solvent | Yield | β:α |
|---|---|---|---|
| $(NH_4)_2HPO_4$ | MTBE | 70% | α:β > 10:1 |
| PMP | MTBE | 77% | α:β = 1:10 |

We conducted DFT calculation to gain additional mechanistic insights, employing **27** and acetate **28** as the model substrates. We found the reaction of acetate anion with **27** is rather rapid, with an activation energy of 5.6 kcal/mol. This energy is significantly lower than the epimerization of **30** to **TS-IV**. Thus, the formation of beta-configured product could be a result of kinetic trap of the glycosyl iodide. We reason in the presence of PMP, a significant portion of carboxylic acid is deprotonated and the resulting anion is the real nucleophile, accounting for the high beta-selectivity observed in the case of **24**+**17**→**18i** and **25**+**17**→**26** in Scheme 2. We cannot rule out the intermediacy of epoxide in our original proposal, though.

## Scheme 6. Computed reaction pathway.



In conclusion, we developed a simple and general method to achieve unprotected, 1,2-*trans* (β-) glycosylation of carboxylic acids. The reaction employs allyl glycosyl sulfones as donors, proceeds under visible light irradiation and passes through glycosyl radical intermediates. The reaction is stereoconvergent, and a stereochemical mixture of donors can be employed. No protecting group is needed, which proves convenient for making structurally complex and delicate glycosylated products. It tolerates a wide variety of functional groups and is amenable to the direct glycosylation of commercial drugs and bioactive natural products, including paclitaxel. Experimental and theoretical studies provide insights into the stereochemical origin of this reaction. Besides the possible involvement of epoxide intermediates, kinetic trap of the axially configured glycosyl iodide by carboxylate anion could be another reason for the observed β-selectivities.

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