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Direct and efficient synthesis of nucleosides through the ortho-(tert-butylethynyl)phenyl thioglycosides (BEPTs) protocol

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Nucleosides are highly biologically relevant compounds, and are widely clinically used as drugs for the treatment of virus/bacteria infections and cancers. However, efficient chemical synthesis of nucleoside is highly difficult due to the low reactivity of nucleobases acceptors, challenging the existing synthetic protocols. Here we show an alternative synthetic protocol with judiciously designed o-(tert-butylethynyl)phenyl thioglycosides (BEPTs) as donors. The protocol is featured by stable glycosylation donors and high efficiency, direct glycosylation without the need for preactivation/silylation of nucleobases, broad substrate scope, capacity in furnishing 2-deoxy-nucleosides, cost efficiency, scalability, and significantly improved reaction speed, and exhibits favorable and profound solvent effects for hexafluoroisopropanol (HFIP). To check the practicality of the protocol, efficient preparation of angustmycin A and dJ is accomplished. The reaction mechanisms are systematically investigated, providing deep insights to the BEPT protocol.

Nucleosides play vital roles in a myriad of physiological processes, including enzyme regulation and metabolism, cell signaling, as well as DNA/RNA synthesis. It is therefore not surprising that nucleoside derivatives mimicking their endogenous counterparts have been widely used for disease treatment through various functional mechanisms, including DNA/RNA synthesis inhibition[1] and gene interference (gene silence and RNA interference)[2,3]. For instance, nucleoside derivatives account for almost half of the available antiviral medicines[4,5], while 15 nucleosides have been approved by the FDA for clinical cancer chemotherapy[5–7]. Nucleoside derivatives have also contributed greatly to curb the epidemic of COVID-19, as many FDA-approved and clinically tried anti-COVID-19 drugs are nucleosides (remdesivir and molnupiravir)[8,9]. Meanwhile, nucleosides creating artificial extra base pairs beyond A-T and G-C occupy the central position in explorations of the genetic alphabet expansion, opening the door to establish novel biological systems and next-generation biotechnologies[10]. Moreover, as secondary metabolites, complex nucleosides with evident structural variations from endogenous nucleosides have been demonstrated to exhibit significant bioactivities, especially antibacterial and antifungal activities[11]. As such, the multifunctionality of nucleoside derivatives warrants the intensive efforts devoted to the development of efficient protocols for nucleoside preparation, and synthesis of noncanonical nucleoside derivatives has been deemed as an emerging area of high potential impact recently[12]. Continuous endeavors have culminated in the establishment of three synthetic strategies[13,14]: N-glycosylation, sugar-ring construction, as well as enzymatic transglycosylation strategies.

As the canonical and mainstay strategy and represented by the Vorbruggen protocol[15], the anomeric cation-involved *N*-glycosylation strategy has witnessed tremendous progress, as evidenced by the applied glycosyl donors evolving from conventional glycosyl acetates[15], thioglycosides[11], and trichloroacetimidates (TCI)[16] to the

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cutting-edge glycosyl *o*-alkynylbenzoates (ABzs)[17], 3,5-dimethyl-4-(2′-phenylethnylphenyl)phenyl (EPP) glycosides[18], glycosyl o-(1-phenylvinyl)benzoate (PVB)[19], as well as glycosyl carbonate donors (Fig. 1)[20]. Additionally, with the renaissance of the radical-based glycosylation[21], N-glycosylations entailing glycosyl anomeric radical species also appeared sporadically[22,23]. Although big stride has been made, the drawbacks, such as a stoichiometric promoter system, highly difficult-to-operate nucleobase preactivation (silylation), limited substrate scope, sluggish reaction speed, and unsatisfactory synthetic efficiency, need to be appropriately tackled to improve the synthetic efficiency. The sugar-ring construction strategy relies on intramolecular glycosylation[24], intramolecular substitution[25], RCM reaction[26], or iodocyclization to construct the sugar ring[27,28]. However, the challenging C-N bond formation cannot be eliminated; instead, it is moved before sugar-ring fabrication. Therefore, the drawbacks associated with the N-glycosylation strategy still remain in the sugar-ring construction strategy. In addition, the synthesis of ring-closure precursor and post-ring-closure modifications is generally a multistep process, further compromising the synthetic efficiency. As a useful complement to the chemical strategies, the enzymatic transformation strategy has made substantial progress in the past decades. Nevertheless, the high reliance on two kinds of enzymes, the nucleoside 2′-deoxyribosyltransferases (NDTs) and nucleoside phosphorylases, some of which are difficult to access, seriously restricts the synthesis scale and product diversity[14]. Under such a context, novel synthetic protocols exquisitely solving the drawbacks mentioned above are highly desirable[29].

In this work, inspired by the successful application of o-methoxycarbonylethynylphenyl thioglycosides (MCEPTs) in N,O-glycosides synthesis[30] and with o-(tert-butylethynyl)phenyl thioglycosides (BEPTs) as donors, an alternative BEPT protocol for efficient nucleosides synthesis is established. The BEPT protocol is distinguished from existing methods by enhanced efficiency, expanded substrate scope, dramatically simplified experimental operation, lowered catalyst loading, and accelerated reaction speed. Combined with the saccharide C-O bond editing techniques[31], stereoselective and concise synthesis of the challenging 2′-deoxy nucleoside derivatives was also achieved via the BEPTs protocol[32]. Through the substrate scope investigations, the beneficial solvent effects of hexafluoroisopropanol (HFIP)[33] in nucleoside synthesis, including dramatically improving the reaction speed in the protecting group (PG)/solvent procedures and accommodating free uracil derivatives as viable acceptors in the solvent procedure, are disclosed. The protocol is amenable to scale-up synthesis of nucleosides, and is successfully applied in efficient and convergent/flexible syntheses of the challenging but biologically relevant nucleosides angustmycin A, dJ, and dJ 3′-deoxy analog. Moreover, the underlying reaction mechanisms are also investigated, providing deep insights into the BEPT protocol.

Results and discussion

The investigation commenced with glycosylation of **2a** with MCEPT donor **1a'** under the catalysis of $Ph_3PAuNTf_2$ (Fig. 2A). Unexpectedly, no desired glycosylation product **3a** was detected in the presence of 0.2 equiv of Au(I) catalyst in 4 h, and all donors were recovered. The failure

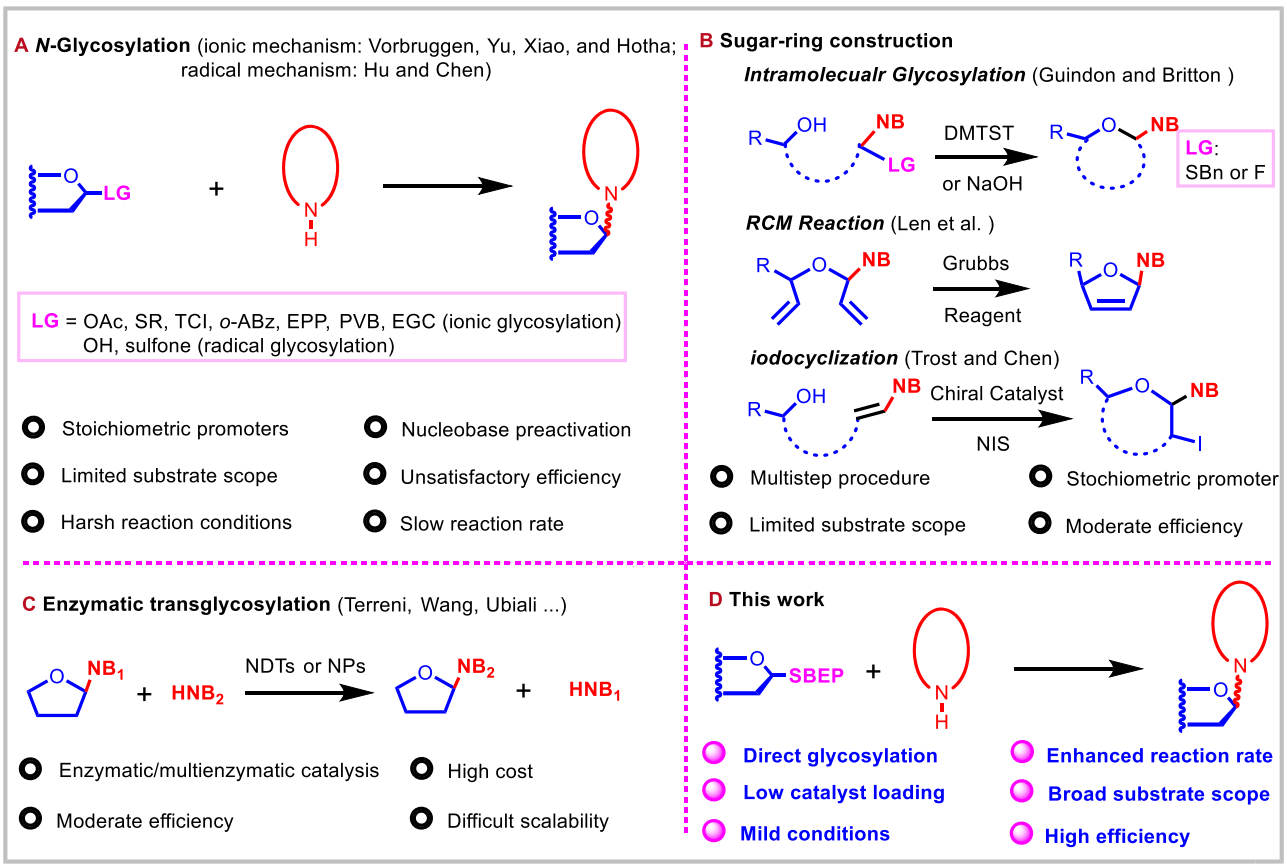

Fig. 1 | Existing strategies for nucleoside synthesis and the BEPT protocol. **A** N-glycosylation strategy via either ionic or radical mechanisms (LG leaving group, o-ABz ortho-alkynylbenzoyl, EPP 3,5-dimethyl-4-(2′-phenylethnylhenyl)phenyl, PVB ortho-(1-phenylvinyl)benzyl, EGC ethynylcyclohexyl glycosyl carbonate). **B** Sugar-ring construction strategy (LG leaving group, NB nucleobase). **C** Enzymatic transglycosylation strategy (NB nucleobase). **D** The BEPT protocol (BEP o-tert-butylethynylphenyl).

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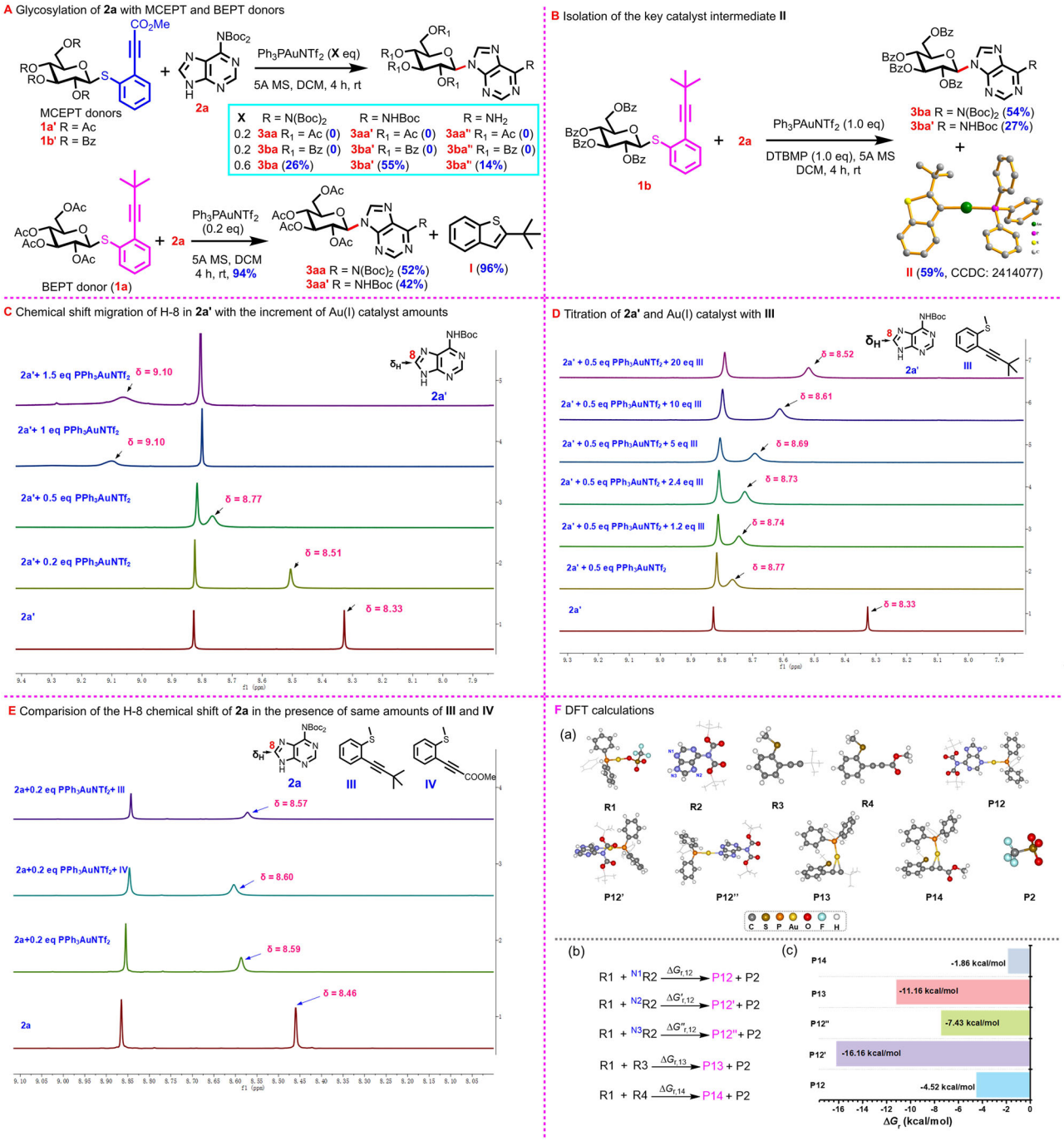

Fig. 2 | Mechanism elucidation of the BEPT protocol in nucleoside synthesis. **A** Glycosylation of **2a** with MCEPT and BEPT donors (MCEPT o-(methoxycarbonylethynylphenyl)thio). **B** Isolation of the key catalyst intermediate **II**. **C** The chemical shift migration of H-8 of **2a'** with the increment of Au(I) catalyst amounts. **D** Titration of **2a'** and Au(I) catalyst (0.5 equiv) with **III**. **E** Comparison of the chemical shifts of H-8 in **2a** in the presence of the same amount of **III** and **IV** (2.0 equiv). **F** DFT calculations (The calculations were conducted using Gaussian 09D).

of donor **1a'** in glycosylation of adenine derivative **2a** was attributed to the electron-withdrawing effect of the methoxycarbonyl group in MCEPT donor, which decreased the electron density of C≡C triple bond thus weakening its coordination with Au(I) catalyst; meanwhile, as a competitive interaction the coordination between Au(I) catalyst and basic nucleobase acceptor predominated thereby halting the glycosylation reaction. Nevertheless, the methoxycarbonyl group has been proven essential in validating o-alkynylphenyl thioglycoside-type donors as it provides critical stabilization to the pivotal catalyst species—the benzothiophen-3-yl gold(I) complex—to suppress orthoester by-product formation[30]. This dilemma raised the question of whether a steric alkyl substituent, rather than an electron-withdrawing group, could simultaneously stabilize the benzothiophen-3-yl gold(I) intermediate and enhance the affinity between C≡C and Au(I) catalyst so as to validate a novel type of glycosylation donor with mitigated undesired interference of nucleobase acceptors. To test this hypothesis, the methoxycarbonyl group of **1a'** was replaced with a bulky but electron-donating *tert*-butyl (^{t}Bu) group, resulting in BEPT donor **1a** (see Supplementary Information), which was then subjected to condense with **2a** under otherwise identical conditions as used for **1a'**. Pleasantly, the desired glycosylation products **3a** and **3a'** (with one tert-butoxycarbonyl (Boc) group cleaved) were obtained in a 94% combined yield (**3aa**: 52%, **3aa'**: 42%) along with

the departed leaving group **I** (96%). The high glycosylation efficiency of BEPT donor **1a** with **2a** verified the conjectured favorable effects of the ^{t}Bu substituent in BEPT donors, that is, the stabilizing effect on pivotal Au(I) catalyst intermediate and the activating effect on leaving group, with the former fully corroborated by the isolation and thorough characterization of the *tert*-butyl-substituted benzothiophen-3-yl gold(I) intermediate **II** (CCDC: 2414077, Fig. 2B). To shed further light on the reaction mechanism, a series of NMR experiments were conducted. First, the interaction between nucleobase **2a'** and Au(I) was investigated (Fig. 2C). Upon addition of 0.2 equiv of Au(I) catalyst to the solution of **2a'** in deuterated chloroform in an NMR tube, an evident downfield shift of H-8 from 8.33 to 8.51 ppm was detected, demonstrating the complexation between Au(I) and **2a'**. The H-8 signal shifted gradually to the downfield with the amount of Au(I) catalyst increased and finally reached 9.10 ppm at 1.0 equivalent of catalyst. Increasing the catalyst amounts from 1.0 to 1.5 equivalents did not cause the signal of H-8 to shift downfield further, indicating the stoichiometry of catalyst and nucleobase in Au(I)-nucleobase complex was 1: 1. According to the donor design considerations and results of model reaction, the BEPT donor should compete with nucleobase to coordinate with Au(I) catalyst, leading to donor activation and nucleobase release simultaneously and ultimately product formation. To confirm this, NMR titration of **2a'** and Au(I) catalyst (0.5 eq) with dramatically simplified BEPT donor **III** (see Supplementary Information) was performed. Indeed, with the addition of **III**, the H-8 signal shifted upfield from 8.77 to 8.52 ppm (20 equivalent of **III**), demonstrating the gradual release of nucleobase **2a'** under the effect of **III** (Fig. 2D). For direct comparison, solutions of **2a** in the presence of 0.2 equivalents of Au(I) catalyst were added 2.0 equivalents of **III** and simplified MCEPT donor **IV** (see Supplementary Information), respectively. Instead of upfield shift, a slight downfield shift of H-8 of **2a** was observed in the presence of **IV** indicating the negligible interaction between **IV** and Au(I) catalyst in the presence of nucleobase (Fig. 2E). From Fig. 2C–E, an interesting phenomenon that even under the effect of 0.2 or 0.5 equiv of Au(I) complex only one species of nucleobase instead of two was detected from the NMR spectra. Given the 1:1 stoichiometry of catalyst and nucleobase in Au(I)-nucleobase complex determined in Fig. 2C, this observation is really intriguing. The rapid reversible coordination/dissociation between the Au(I) catalyst and nucleobase might be invoked to interpret this abnormal observation, which made the free and coordinated **2a'**/**2a** indistinguishable in the NMR time scale, thus presenting average spectra in all cases. Along this line, a conclusion that the deactivation of Au(I) catalyst by nucleobase acceptor is not the irreversible poisoning but the rapid reversible coordination/dissociation, which considerably decreases the effective concentration of catalyst, could be deduced. Indeed, under 0.6 equiv of Au(I), glycosylation of **2a** could also be achieved by the MCEPT donor **1b'** to deliver the nucleosides in a 95% combined yield (Fig. 2A). DFT calculations were subsequently carried out to decipher the coordination pattern of Au(I) catalyst and **2a** and to determine the affinity difference between Au(I) catalyst and **2a**/**III**/**IV**, respectively (Fig. 2F). Although N3, N7, and N9 (corresponding to *N*1-3 in the DFT study) all could coordinate with Au(I) catalyst, the N7-liganded complex **P12'** exhibited the highest stability with the ΔG being −16.16 kcal/mol. Compound **III** could also coordinate with Au(I) catalyst efficiently as the coordination ΔG reached as low as −11.16 kcal/mol (**P13**), higher than *N*7-ligated complex but remarkably lower than *N*3- and *N*9-ligated complexes (**P12** and **P12''**). In contrast, the coordination of **IV** with Au(I) catalyst was much less thermodynamically favorable than **III** (**P14**, ΔG = −1.86 kcal/mol), disclosing the underlying factor responsible for the invalidity of MCEPT donor in nucleobase glycosylation at low catalyst loading.

Combined with the control reactions, the NMR experiments, and the DFT calculations illuminated the mechanism of N-glycosylation with BEPT donor, and meanwhile, spurred the following in-depth explorations to establish the BEPT-based protocol for efficient nucleoside preparation.

Encouraged by the promising results of the model reaction, the substrate scope of the BEPT-based nucleoside synthesis protocol was checked. As direct glycosylation of purine nucleobases avoiding prior activation/silylation could be realized by using Boc-protected purine derivatives as acceptors (PG procedure), the substrate scope exploration began with purine nucleobases (Fig. 3). Adenine and guanine derivatives **2a**-**f**, featuring di-Boc-protected exocyclic amino groups, were chosen as representative purine acceptors to condense directly with BEPT donors derived from a variety of sugars, including D-glucose (**1a**-**c**), D-galactose (**1d**), D-mannose (**1e**), L-rhamnose (**1f**), L-arabinose (**1g**), D-xylose (**1h**), D-ribose(*f*) (**1i**), L-arabinose(*f*) (**1j**), D-fructose(*f*) (**1k**), and disaccharide lactose (**1l**), under the catalysis of Au(I) complex without need for purine base activation in advance. The di-Boc-protected nucleosides (**3aa**-**3lf**) and their mono-Boc-protected analogs (**3aa'**-**3lf'**) were obtained in good to excellent combined yields (59%–99% yields). It should be pointed out that the glycosylation systems were clean, and the di-Boc and mono-Boc nucleosides could be easily separated by silica gel column chromatography due to the disparate polarity. Interestingly, a conformation flip from $^{4}C_1$ to $^{1}C_4$ was observed for the mannosyl moieties in **3ec**/**3ec'** and **3ed**/**3ed'**. Similar phenomenon was also detected in rhamnosyl nucleosides **3fb'**, **3fc**/**3fc'**, and **3fd**, entailing $^{1}C_4$ to $^{4}C_1$ conformation flip ($J_{1',2'} > 5.0$ Hz). Ketosyl BEPT glycoside **1k** served also as a competent donor to glycosylate di-Boc-protected purines, providing **3ka**/**3ka'** and **3kd**/**3kd'** in 96% and 95% yield, respectively. Noticeably, lactosyl BEPT glycoside **1l** also proved to viable donor, furnishing disaccharide nucleosides **3lf**/**3lf'** in good yield (79%). Apart from the couplings of **1d**/**2a** and **1l**/**2f**, which required 24 h to reach completion, all other tested condensations finished within 4 h, faster than related Au(I)-catalyzed nucleoside synthesis protocols[17,20]. Moreover, some glycosylation reactions, such as those involving the donor/acceptor pairs of **1b**/**2b**, **1b**/**2c**, **1b**/**2d**, **1c**/**2d**, **1d**/**2b**, and **1i**/**2d**, were completed in just 1 h, highlighting the high reaction rate of the BEPT protocol. The isolation of mono-Boc-protected nucleosides implies the high propensity of the di-Boc-protected amino group to undergo one Boc cleavage under mild conditions, which could be exploited to simplify product purification by post-glycosylational one-pot conversion of di-Boc- to mono-Boc-protected products. Specifically, upon completion of glycosylation, direct addition of silica gel to the reaction mixture of **1j** and **2a** and stirring delivered mono-Boc **3ja'** (74%) as the only product, as with the case for the coupling of **1j** and **2d** (**3jd'**: 93%). Remarkably, synthesis of purine-type nucleosides through the BEPT protocol could also be achieved under dramatically reduced-catalyst loading (0.02 or 0.04 eq) without an evident drop in yields (above 84%), albeit in extended reaction time (8–48 h). Fortunately, the prolonged reaction time unified the glycosylation products rendering mono-Boc nucleosides (**3bb'**, **3cc'**, **3fb'**, **3ib'**, **3id'**, **3jb'**, **3jd'**, and **3lb'**) as the only products, except for **3fd'** and **3ld** which were accompanied by NH_2-free nucleoside **3fd''** (92% combined yield) and **3ld'** (84% combined yield), respectively. Further investigations revealed that the PG procedure of the BEPT protocol enjoyed a profound solvent effect; with HFIP/dichloromethane (DCM) as solvent[34], the rate of the couplings was dramatically enhanced making the couplings conducted under reduced-catalyst loading (0.02–0.04 equiv) to complete in 1 h to deliver the desired products in good to excellent yields (above 59% for **3bb**/**3bb'**, **3ec**/**3ec'**, **3fd**/**3fd'**, **3hd**/**3hd'**, **3ib**/**3ib'**, **3kc**/**3kc'**, and **3lf**/**3lf'**). The favorable solvent effect of HFIP could be attributed to its acidity[34], which facilitates the protodeauration, thus improving the catalyst turnover[17]. All the tested donors were demonstrated to be exceptionally stable, remaining virtually intact even after a prolonged time of storage at room temperature without special protection from air and moisture. The *N*-9 regioselectivity was determined by the ^{13}C

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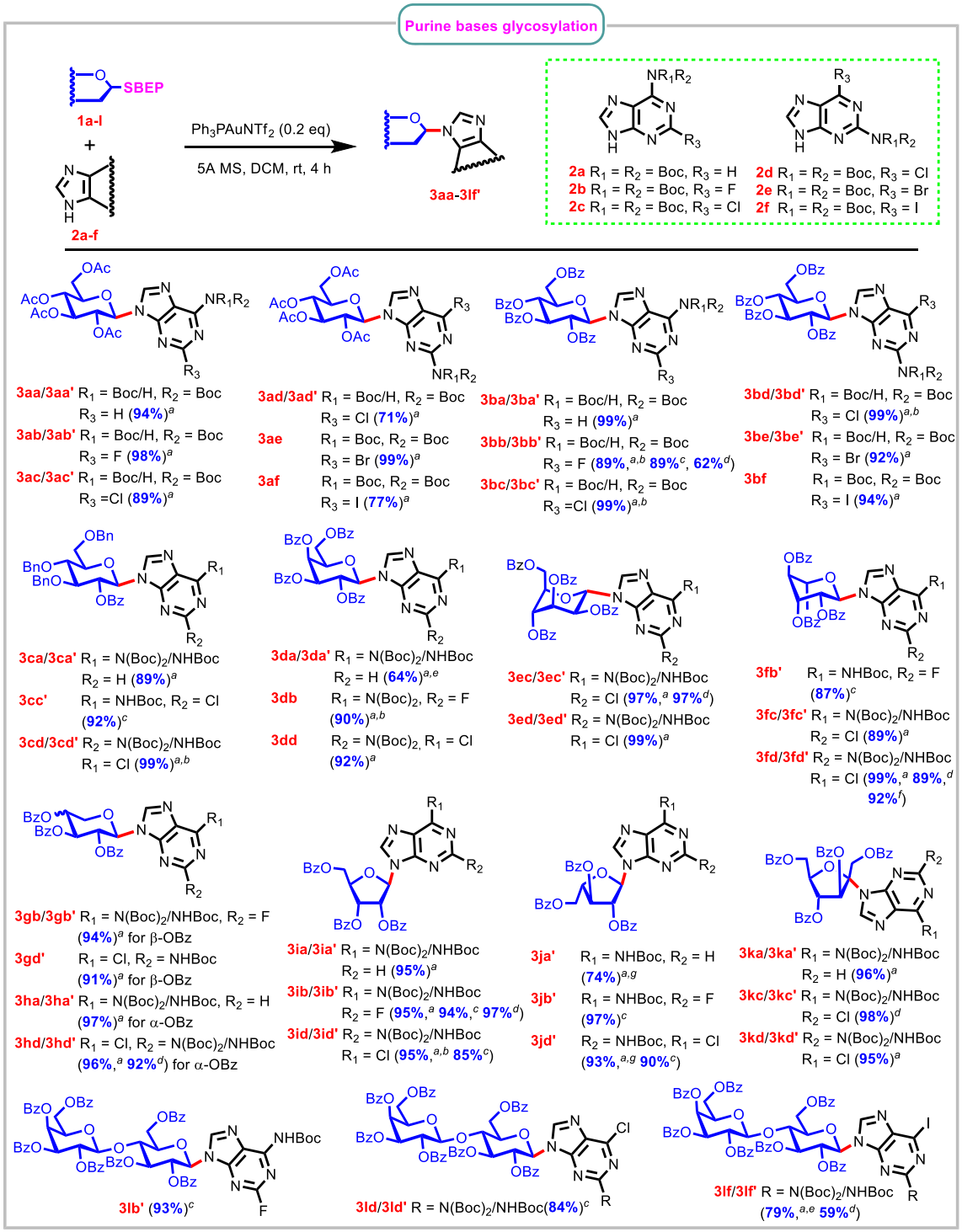

[a]The combined yield of di-Boc and mono-Boc nucleosides under catalysis of 0.2 eqvalents of Au(I) catalyst (for details, see SI). [b]The reaction time was 1 h. [c]Yield of mono-Boc nucleoside obtained under reduced catalyst loading (0.02 eq or 0.04 eq, see SI). [d]The combined yield of di-Boc and mono-Boc nucleosides obtained in a mixed solvent of DCM and HFIP (v/v = 4 : 1) under reduced catalyst loading (0.02 or 0.04 eq) in 1 h (see SI).[e]The reaction time was 24 h. [f]The combined yield of mono-Boc and Boc-free nucleosides under the reduced catalyst loading (see SI) [g]The yield was obtained through direct treatment of the glycosylation mixture with silica gel (stirred at room temperature for 8 h).

Fig. 3 | Direct synthesis of purine-type *N*-glycosides through the PG procedure of the BEPT protocol. Boc-protected purine derivatives were selected as acceptors. Boc butoxylcarbonyl.

chemical shift of C-5 in nucleobase (bigger than 120 ppm)[35], which was further confirmed by HMBC (see Supplementary Information).

Direct glycosylation of pyrimidines, omitting the prior activation/silylation, has not been documented. Akin to purine derivatives, the PG procedure was attempted to realize the direct synthesis of pyrimidine-type nucleosides. p-Methoxybenzyl (PMB) group was selected as a PG for the endocyclic N3 of uracil derivatives, while Boc was chosen as PG for the exocyclic NH_2 of cytosine. Thus, N3 PMB-protected uracil (**4a**), thymine (**4b**), 5-fluorouracil (**4c**), and di-Boc-protected cytosine (**4d**) were selected to react with various BEPT donors derived from both

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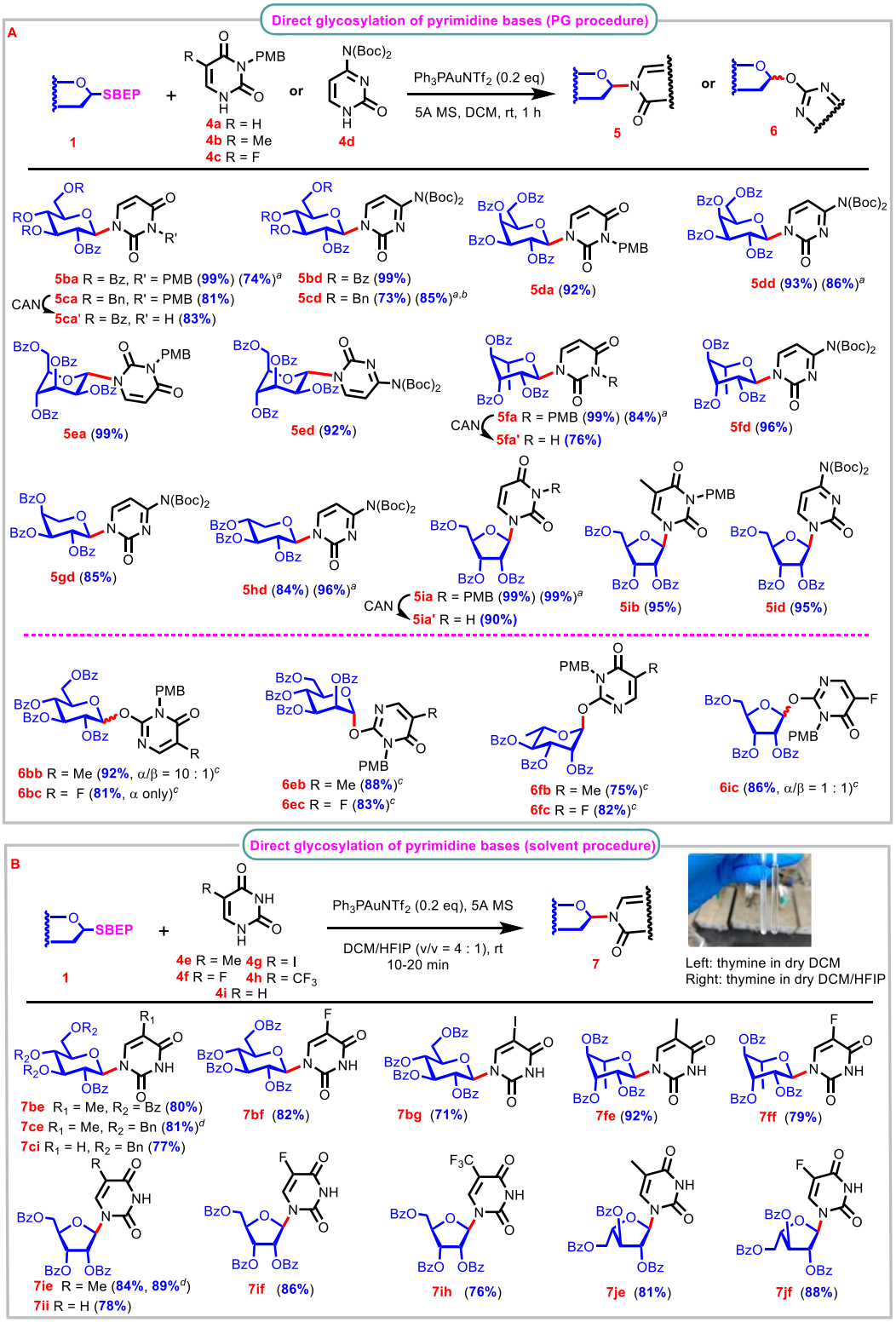

[a]Yield was obtained under the reduced catalyst loading (8 h, see SI). [b]Reduced catalyst loading in 1 h with DCM/HFIP as solvent. [c]4A MS was used as the desiccant and the reaction time was 4 h. [d]Under the catalysis of 0.02 equiv of catalyst (see SI).

Fig. 4 | Direct synthesis of pyrimidine-type glycosides through the BEPT protocol. A Direct glycosylation of pyrimidine bases through the protecting group (PG) procedure of the BEPT protocol (PMB-protected pyrimidine bases were selected as acceptors. PMB *p*-methoxybenzyl. **B** Direct glycosylation of pyrimidine bases through the solvent procedure of the BEPT protocol (A mixture of DCM and HFIP (v/v = 4:1) was used as reaction media. DCM dichloromethane, HFIP hexafluoroisopropanol.

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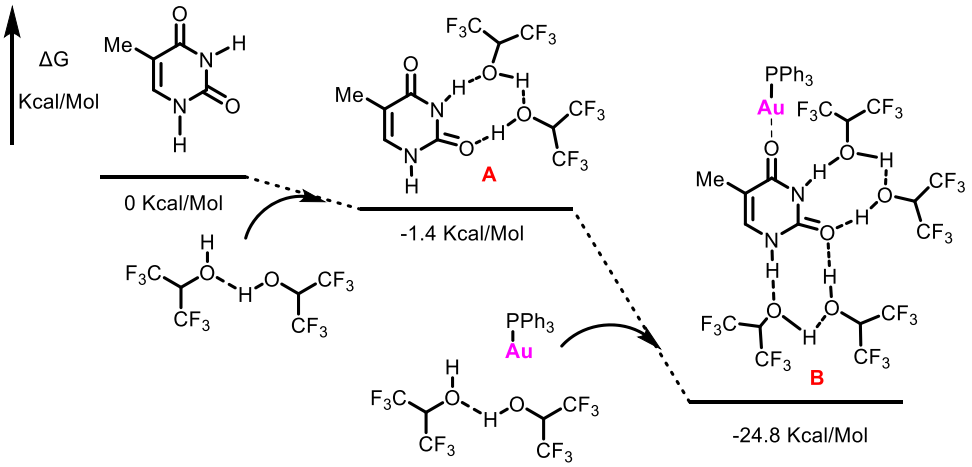

Fig. 5 | DFT calculations (The calculations were performed with B3LYP/def2-SVP//M06-2X/def2-TZVP).

hexoses and pentoses (in pyranosyl or furanosyl form, Fig. 4A). With **4a** and **4d** as acceptors, all tested donors presented *N*-glycosides **5ba**-**5id** with yields exceeding 73% in 1 h under the catalysis of 0.2 equivalents of Au(I) complex, achieving direct, swift, and highly efficient synthesis of pyrimidine-type nucleosides. Sugar conformation flips were also noticed for *N*-glycosides **5ea**, **5ed**, **5fa**, and **5fd**, derived from D-mannosyl (**1e**) and L-rhamnoseyl (**1f**) BEPT donors, as confirmed by ^{1}H NMR spectra ($J_{1',2'} > 5.0$ Hz) and single crystal X-ray diffraction analysis (CCDC: 2401831 for **5fa**). In addition, mono-Boc products were not detected when **4d** was used as the acceptor. In sharp contrast, when **4b**,**c**, the 5-substituted analogs of **4a**, were used as acceptors, the *O*-glycosides **6bb**-**6ic** were isolated (above 75% yields), as determined by the ^{13}C NMR (above 90 ppm for the anomeric carbons) and HMBC (correlations between anomeric H and C2 of nucleobase, yet non-correlations between anomeric H and C6 of nucleobase). Moreover, although equipped with C2-*O*-appended benzoyl groups amenable to exert neighboring group-participation effect, perbenzoylated glucosyl and ribofuranosyl BEPT donors **1b** and **1i** afforded **6bb**/**6ic** as mixtures of α/β isomers, while **6bc** α-exclusively. Prolonging the reaction time of **1b** and **4b** to 12 h under otherwise identical conditions allowed for the generating α-**6bb** exclusively in high yield (90%), while 0.02 equivalents of catalyst afforded β-**6bb** only (see Supplementary Information). These results suggest an in situ epimerization of β-isomer to α-isomer during glycosylation reaction, presumably through the sugar-ring opening/reclosing (at C1-O5 bond) mechanism[36]. The generation of O-glycosides instead of *N*-glycosides was ascribed to the steric hindrance caused by N3- and C5-located substituents, which made *N*1 difficult to access. Thus, even under the conventional silylation/glycosylation conditions, the condensation between **1b** and **4b** still gave O-glycoside as the major product (see Supplementary Information). However, an exception was also observed when **4b** was condensed with ribofuranosyl BEPT donor **1i**, whence N-glycoside **5ib** was secured (95%), presumably due to the synergy of the high glycosylation potential of **1i** and ameliorated reactivity of **4b** with an electron-donating methyl substituent. The PMBs in N-glycosides could be smoothly cleaved under the effect of ceric ammonium nitrate, as exemplified by **5ca**, **5fa**, and **5ia**, which delivered **5ca'**, **5fa'**, and **5ia'** smoothly. On the contrary, attempts to remove the PMBs in O-glycosides met with failure, and glycosidic linkage rupture occurred prior to PMB cleavage. Efforts to convert O-glycosides to the corresponding *N*-glycosides under various conditions also proved futile, although it is well known that the O-glycosides can act as intermediates in nucleoside synthesis. Synthesis of pyrimidine-type nucleosides through the PG strategy of the BEPT protocol could also be conducted under reduced-catalyst loading (0.02 eq) to yield the desired nucleosides in good to excellent yields in 8 h (over 74% yield for **5ba**, **5cd**, **5dd**, **5fa**, **5hd**, and **5ia**), which could be shortened to 1 h in DCM/HFIP when **4d** was used as acceptor (**5cd**, 85%).

In continuous pursuit of direct and efficient synthesis of 5-substituted uracil nucleosides, a solvent procedure with HFIP as co-solvent was explored subsequently (Fig. 4B). The choice of HFIP is not only because of its verified beneficial effects on purine-type nucleoside synthesis but also because its well-known talent in H-bond formation, which at least could tackle the solubility problem of pyrimidine bases[34]. Indeed, free thymine was completely dissolved in DCM/HFIP leading to a homogeneous solution, while forming a suspension in pure DCM (Fig. 4B). Pleasantly, using DCM/HFIP as reaction media, glycosylation of **4e** with **1b** proceeded smoothly under the catalysis of Au(I) complex at room temperature to yield **7be** in 80% yield; however, unexpectedly, the coupling reached completion in only 10 min. The procedure enjoyed broad substrate scope in terms of both glycosyl BEPT donors and 5-substituted uracil acceptors, yielding nucleosides **7bf**-**7jf** in 71%–92% yields in 10–20 min. In fact, free uracil **4i** also proved a viable acceptor, providing the desired nucleosides **7ci** and **7ii** in good yield. Subsequently, the reduced-catalyst-loading version of the solvent procedure was briefly studied, and high efficiency was maintained (**7ce** and **7ie**). Interestingly, although free **4e**-**i** were selected as glycosylation acceptors, no N3-regiomers were detected[37]. Directly using unprotected nucleobases as glycosylation acceptors, nucleoside synthesis through the solvent procedure eliminates not only silylation/activation processes but also PG manipulations, further streamlining the chemical synthesis of nucleosides. Again, conformational switch of D-mannosyl as well as L-rhamnosyl residues was noticed in the pyrimidine series nucleosides. Besides, BEPT donors were also integrable to the one-pot silylation/glycosylation procedure to give 5-substituted uracil-type nucleosides **7be**-**7if** efficiently (above 86% yields), highlighting the versatility of the BEPT glycosylation method (see Supplementary Information).

The unexpected beneficial effects of HFIP in the solvent procedure were tentatively ascribed to its strong H-bond donation ability[34], triggering the formation of favorable intermolecular H-bond systems between uracil derivatives and HFIP. This assumption was supported by DFT calculations (Fig. 5). In the presence of HFIP, an 8-membered intermolecular H-bond system was formed between thymine and HFIPs, leading to **A** ($\Delta G = -1.4$ kcal/mol). Upon addition of the catalyst, the Au(I) complex promoted the formation of another 8-membered intermolecular H-bond system, resulting in **B**, which was highly thermodynamically favored ($\Delta G = -24.8$ kcal/mol). The DFT calculations were further corroborated by the following 2D NMR experiments. In the absence of Au(I)-catalyst, 1-NH/HFIP OHs, 3-NH/HFIP OHs, and 3-NH/HFIP C-H correlations were detected in the NOESY spectrum, demonstrating the existence of **A**, which was further supported by the

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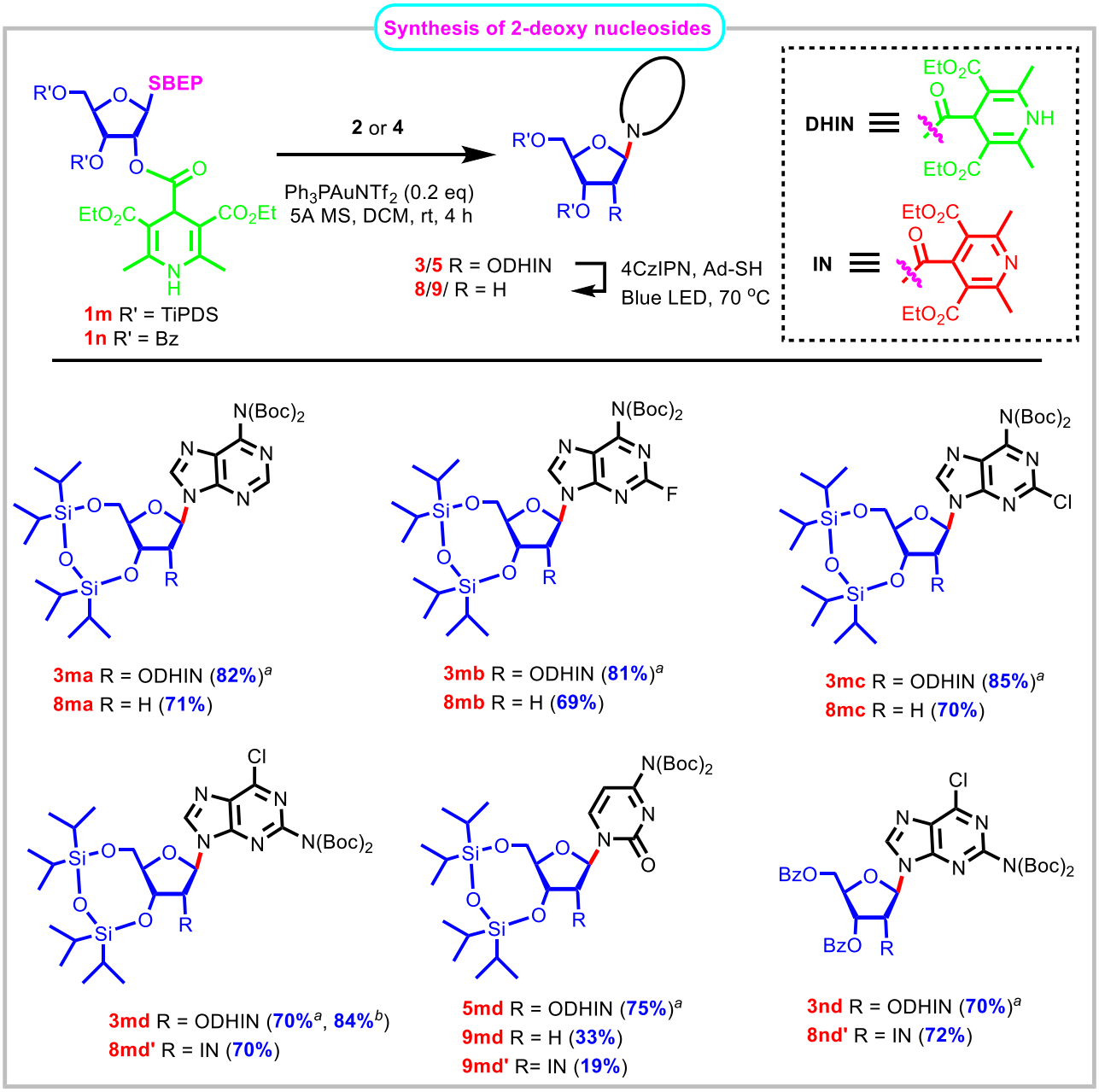

[a]Yield only for di-Boc glycosylation product. [b]The combined yield of mono-Boc- and di-Boc-protected products at 0.02 equiv of catalyst in DCM/HFIP in 30 min.

Fig. 6 | Synthesis of 2′-deoxynucleoside derivatives by the combination of BEPT protocol and photocatalyzed C–O bond editing techniques (1,4-dihydroisonicotinoyl (DHIN) was used as a stereo-controlling and deoxygenation-initiating group, and the direct saturation of the DHIN group to isonicotinoyl (IN) group was found to be the major side reaction).

evident correlation between 1-NH and 3-NH enabled by the flexibility of 1-NH (see Supplementary Information). Under the effect of Au(I) catalyst, the emergence of the correlation between 1-NH and HFIP C-H and the disappearance of the correlation between 1- and 3-NHs were detected. In addition, the correlation between phenyl ring of the catalyst ligand and thymine methyl group in the NOESY spectrum revealed the coordination of pyrimidine base to the Au(I) catalyst through the *C*4-carbonyl oxygen. All of these spectroscopic proofs pointed to the formation of **B**. Effected by the two flanked carbonyl groups, the acidity of 3-NH should be much higher than that of 1-NH, which would inevitably make the 3-NH-involved cyclic H-bond system much stronger than the 1-NH-engaged cyclic H-bond system, thereby assuring the high *N*1 regioselectivity of the glycosylation reactions. Moreover, in the 1-NH-involved cyclic H-bond system, the 1-NH acted as a H-bond donor to form the favorable H-bond with appropriate strength, thus resulting in improved reactivity of 1-NH in nucleoside synthesis[38].

Despite continuous efforts, the stereoselective synthesis of 2′-deoxy nucleosides remains a prominent challenge in carbohydrate chemistry[39]. The advent of the BEPT protocol provided a solution to this chronic problem upon cooperation with the photocatalyzed sugar C–O bond editing method[31], with 1,4-dihydroisonicotinoyl (DHIN) group as both the stereo-controlling and the deoxygenation-initiating group (Fig. 6). To our pleasure, under the standard

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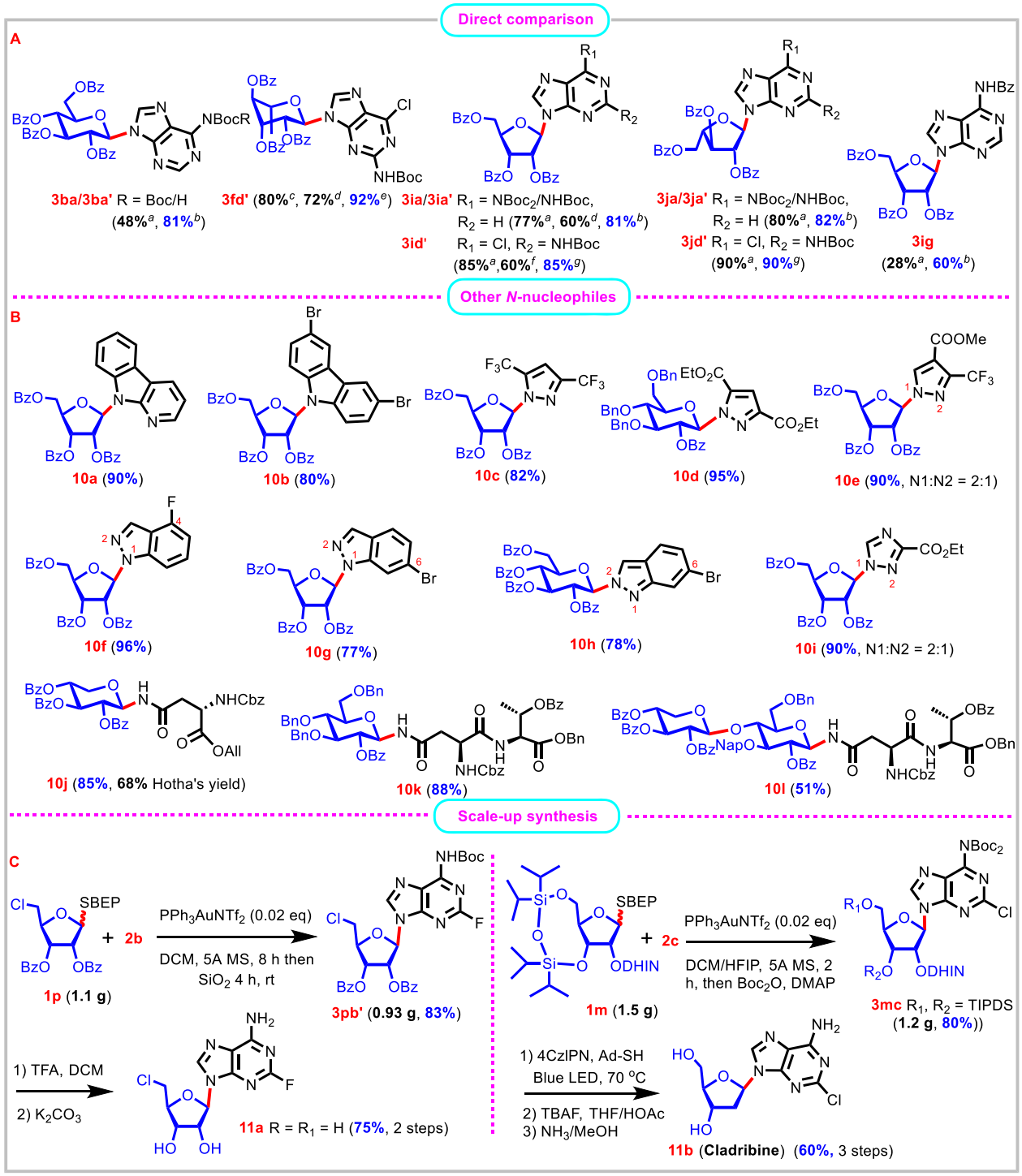

[a]Yield reported in Yu's paper. [b]Yield obtained with our BEPT protocol (PG procedure) under 0.1 equivalents of Au(I) catalysis. [c]Yield reported in Yu's paper with the corresponding peracetylated rahmnosyl Yu donor. [d]Yield reported in Hotha's paper. [e]Yield was obtained with our BEPT protocol (PG procedure) under 0.02 equivalents of Au(I) catalysis. [f]Yield reported by Hotha's paper with the corresponding super-armed donor. [g]Yield was obtained with our BEPT protocol (PG procedure) under 0.04 equivalents of Au(I) catalyst.

Fig. 7 | Examination of the practicality of the BEPT protocol. A Comparison of the BEPT protocol with ABz and EGC protocols (ABz *o*-alkynylbenzoyl, EGC ethynylcyclohexyl glycosyl carbonate). **B** Glycosylation of other *N*-nucleophiles (the chemical structures were unequivocally determined by 1D and 2D NMR). **C** Scalable synthesis of nucleoside drugs (the N-glycosylation steps were conducted on a gram-scale).

conditions, donors **1m**,**n** bearing DHIN group at C2-OH reacted smoothly with purine/pyrimidine acceptors **2**,**4** under the PG procedure to produce **3ma**-**3nd** β-stereoselectively in good yields (70–85% yield). The reaction time could be further shortened to 30 min by applying DCF/HFIP as reaction media even in the presence of 0.02 equiv of catalyst (84% for **3md** and mono-Boc-protected **3md**). Moreover, the subsequent deoxygenation also proceeded uneventfully to give 2′-deoxy-nucleosides **8ma**-**mc** (69–71% yield) under the combined effect of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN), adamantanethiol, and light (467 nm).

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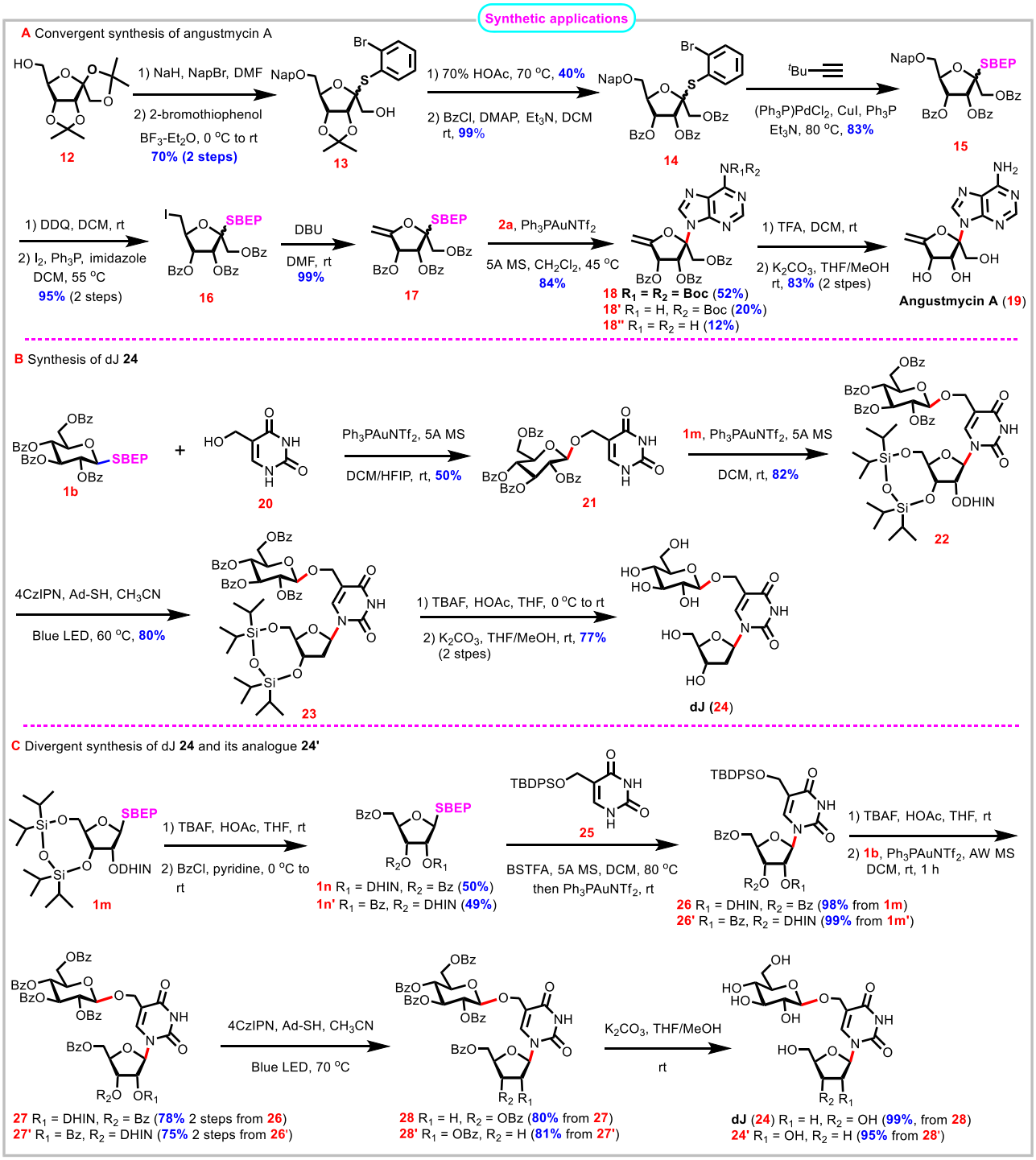

Fig. 8 | Synthesis of augustmycin A (19), dJ (24), and dJ analog (24′). **A** Convergent synthesis of angustmycin A (N-glycosidic linkage construction after exo-glycal fabrication). **B** Synthesis of dJ **24** (the glycosidic linkage construction sequence is O-glycosidic linkage first and then N-glycosidic linkage). **C** Divergent synthesis of dJ **24** and its analog **24′** (the glycosidic linkage construction sequence is N-glycosidic linkage first, followed by O-glycosidic linkage).

Further investigations turned out that the deoxygenation was highly dependent on the nucleobase subunits, with nucleoside **5md** derived from **4d** providing the desired 2′-deoxynucleoside **9md** (33%) accompanied by isonicotinoyl (IN) group-containing by-product **9md′** which was photo-catalytically inert (see Supplementary Information)[40], while nucleosides **3md**/**3nd** derived from acceptor **2d** affording IN-containing by-products **8md′**/**8nd′** completely (70% and 72% yield). Surprisingly, DHIN-containing donors **1m**,**n** could not condense efficiently with free uracil acceptors in HFIP/DCM. As a detour to access the corresponding 2′-deoxy nucleosides, the BEPT-involved one-pot silylation/glycosylation procedure was adopted, and the obtained 5-substituted uridines were successfully converted to 2-deoxy nucleosides under the photocatalytic conditions (62–85% yield) (see Supplementary Information).

For direct comparison of the BEPT protocol with existing catalytic protocols in nucleoside synthesis (the ABz and EGC protocols), syntheses of **3ba**/**3ba′**, **3ia**/**3ia′**, and **3ja**/**3ja′** through the BEPT protocol were repeated under the catalysis of 0.1 equivalents of Au(I) catalyst

(Fig. 7A). For **3ba**/**3ba'**, the BEPT protocol afforded 81% yield of products much higher than that of the ABz protocol (**3ba**, 48% yield)[17], as with the case for the synthesis of **3ia**/**3ia'**, wherein the BEPT protocol provided 81% yield of **3ia**/**3ia'** higher than those of the ABz (**3ia**, 77%)[17] and EGC protocols (**3ia**, 60%)[20]. At the very least, comparable yields of **3ja**/**3ja'** were registered between the BEPT and ABz protocols (82% vs 80%). Even under the decreased catalyst loading (0.04 eq), either comparable or higher yields were still maintained for the BEPT protocol (**3jd'**: 90% vs 90% in ABz protocol; **3id'**: 85% vs 85% in ABz protocol and 60% in EGC protocol with the super-armed donor). The catalyst loading could be further reduced to 0.02 equiv without affecting the superior efficiency of the BEPT protocol over the ABz and EGC protocols (**3fd'**: 92% vs 80% in ABz protocol with peracetylated ABz donor and 72% in EGC protocol). Benzoyl-protected adenine **2g** was not a suitable acceptor in the ABz protocol, and only 28% of **3ig** was isolated; however, 60% yield of **3ig** was obtained in the BEPT protocol.

To further expand the acceptor substrate scope, other N-nucleophiles, including carbazoles, pyrazoles, indazoles, 1,3,4-triazoles, and asparagine derivatives, were briefly explored with the BEPT protocol (Fig. 7B)[41]. Under the catalysis of 0.1 equivalents of Au(I) complex, direct glycosylation of the *N*-heteroaromatic nucleophiles proceeded fluently, delivering **10a-i** in 77–96% yields, among which **10e** and **10i** derived from asymmetrically substituted pyrazole and 1,2,4-triazole were obtained as mixtures of regioisomers. The chemical structures of all the obtained *N*-glycosides were unequivocally determined by 2D NMR (see Supplementary Information). Interestingly, synthesis of indazole-type N-glycosides by means of the BEPT protocol exhibits an evident trend that furanosyl donors give 1-N-glycosides while pyranosyl donors furnish 2-N-glycosides as determined by C3 chemical shift (130 ppm for N1- while 120 ppm N2-products) (see Supplementary Information), exquisitely complementing Taylor's method[29]. The obtained N-glycosides are highly biologically relevant as the glucosyl counterpart of **10e** has been used as a reference in residue analysis and risk assessment of oxathiapiprolin[42], **10f-h** analogs have been demonstrated cytotoxic to various cancer cell lines[43], while **10i** was the precursor to ribavirin, the clinically used antiviral agent with broad spectrum[44]. Meanwhile, the functional groups embedded in N-heteroaromatic moieties, such as fluorine, bromine, as well as the ester group, can facilitate the derivatization of these N-glycosides. Furthermore, the amide of asparagine was successfully glycosylated with BEPT donor **1 h** to give glycosyl amino acid **10j** in 85% yield, much higher than that of the EGC protocol[20], further highlighting the advantage of the BEPT protocol. Similarly, asparagine-containing dipeptide could also be glycosylated with **1c**, and **88%** yield of **10k** was secured. Even for the condensation between disaccharide BEPT donor **1o** and asparagine-embedded tripeptide, 51% yield of **10l** was still obtained.

Scalable synthesis is a widely accepted benchmark to evaluate the practicality of a synthetic method; meanwhile, low catalyst loading makes sense only in the scalable synthesis context. Thus, scale-up synthesis of nucleoside drugs was finally investigated through the BEPT protocol under reduced-catalyst loading (Fig. 7C). The condensation of **1p** (1.1 g) with **2b** in the presence of 0.02 equiv of Au(I) complex yielded **3pb'** efficiently (0.93 g, 83%) after silica gel-mediated product unification. Deprotection under conventional conditions transformed **3pb'** to **11a** (75%, 2 steps). As a promising antitumoral drug candidate, nucleoside **11a** has been proven to exhibit potent antitumor activity against a range of cancer cell lines, particularly the prostate cancer cell line Du-145[45]. Direct glycosylation of **2c** with DHIN-bearing donor **1m** was then carried out under the effect of 0.02 equiv of Au(I) catalyst. Benefited from the reaction speed-enhancing effect of HFIP, the coupling reached completion in 2 h, and 80% yield of **3mc** (1.2 g) was registered after product unification via re-*tert*-butoxycarbonylation. The di-Boc protection greatly facilitated the photocatalyzed deoxygenation step, which was followed by silyl group deprotection and Boc's cleavage to provide cladribine **11b** (60%, 3 steps), the clinically prescribed antitumoral and immunosuppress drug[46].

The practicality of the BEPT protocol was further assessed by the synthesis of intricate but biologically relevant nucleosides, angustmycin A and dJ (Fig. 8). Angustmycin A, a nucleoside cytokinin isolated from *Streptomyces hygroscopicus*[47], proved to possess significant antibacterial[48] and antitumor activities[49]. Glycoside dJ, a unique constituent of the DNA of *Kinetoplastida* and *Euglina*, is vital in unambiguously deciphering the function of base J (β-D-glucosyloxymethyluracil) at the molecular level, which could guide the development of therapies against diseases caused by kinetoplastid flagellates[50]. Equally intriguing are the novel chemical structures of angustmycin A and dJ. Rather than a common sugar motif, angustmycin A contains a 5,6-dehydrated psicofuranosyl moiety, bestowing it with a labile exocyclic double bond as well as a sterically hindered ketose anomeric carbon, which challenges the existing *N*-glycosylation protocols. Similarly, the β-2′-deoxyribofuranosyl *N*-glycosidic linkage combined with the co-existing O-glycosidic linkage also poses considerable obstacles en route to dJ by chemical synthesis[11].

Although chemical syntheses of angustmycin A have been reported[51], current synthetic approaches suffer from evident drawbacks, such as the use of environmentally harmful reagents, limited convergency, and unsatisfactory overall efficiency. Equipped with the BEPT protocol, an attempt to establish an alternative robust route to angustmycin A was made (Fig. 8A). Easily available diactonide-protected psicose **12** was further decorated with a 2-naphthylmethyl (Nap) group, which was followed by simultaneous selective anomeric isopropylidene removal and anomeric *o*-bromophenylsulfenyl group incorporation to afford **13** as a mixture of α/β-isomers (70%). Switching the resting isopropylidenyl PG in **13** to benzoyl (Bz) groups with the neighboring group-participation effect was conducted under the conventional conditions to deliver **14** (40%, 2 steps). Sonogashira reaction transformed the latent donor **14** to active BEPT donor **15** (83%). The stability of the leaving group in **15** allowed for the successive cleavage of the Nap group and iodination of the resulting OH to provide iodide **16** (95%, 2 steps). The following exo-glycal fabrication was achieved by base-mediated elimination to give 5,6-dehydrated psicosyl BEPT donor **17** (99%). Despite the challenges posed by the acid-vulnerable exocyclic double bond and the sterically hindered quaternary anomeric carbon, the coupling between **17** and **2a** proceeded smoothly and stereoselectively under the catalysis of Au(I) complex at 45 °C, and the desired *N*-glycosides **18**/**18′**/**18″** were isolated in a combined 84% yield. Global deprotection entailed Bocs removal as well as esters saponification, converting **18**/**18′**/**18″** to angustmycin A **19** (83%, 2 steps)[52]. Thus, based on the BEPT protocol, a robust synthetic approach to angustmycin A, featuring exo-glycal fabrication prior to *N*-glycosidic linkage construction, was successfully set up (convergent synthesis). Through this approach, augustmycin A **19** was secured in an 11-step longest linear sequence (LLS) with 15% overall yield from **12**.

Relying on 2′-deoxyuridine, chemical synthesis of dJ has also been accomplished[53,54]. Nevertheless, although bypassing the construction of the challenging 2′-deoxy-*N*-glycosidic linkage, the established synthetic route remains lengthy due to tedious PG manipulations. Capitalizing on the BEPT protocol and photocatalyzed sugar C-O bond editing method, concise and facile synthesis of dJ from cost-efficient starting materials was accomplished (Fig. 8B). With DCM/HFIP as the reaction medium, direct glycosylation of 5-hydroxymethyluracil **20** with BEPT donor **1b** occurred preferentially on the primary OH to afford **21** (50%), along with some N,O-bisglycosylated by-product. Subsequent *N*-glycosylation of **21** with ribosyl BEPT donor **1m** in the presence of Au(I) catalyst afforded the *N*,*O*-bisglycosylated product **22**

(82%), primed for photocatalyzed deoxygenation. Under the combined effect of 4CzIPN, Ad-SH, as well as LED irradiation, 2′-deoxygenation of the ribosyl residue, initiated by the 2′-*O*-attached DHIN group, took place fluently to complete the assembly of the protected dJ **23** (80%). Desilylation followed by Bzs saponification realized the full deprotection of **23** to provide dJ **24** (77%, 2 steps). As such, through the approach with *O*-glycosidic linkage construction prior to *N*-glycosidic linkage, dJ was secured through a 5-step LLS in 25% overall yield, whereas the existing route provided the same product in 8% overall yield via a 7-step LLS with 2′-deoxyuridine as starting material.

An alternative approach to dJ with reversed order of glycosidic linkage construction, namely, *N*-glycosidic linkage first, then O-glycosidic linkage, was also devised, giving rise to not only dJ but also its 3′-deoxy analog (Fig. 8C). Taking advantage of the stability of the BEPT donors, the swap of the cyclic tetraisopropyldisiloxane-1,3-diyl (TiPDS) group for two Bzs was conducted on donor **1m**. Surprisingly, notwithstanding the buffered mild desilylation conditions, DHIN group migration from 2-OH to 3-OH took place, providing **1n** and **1n′** in almost equal yields (50% and 49%, respectively), which could be separated chromatographically and were separately advanced to the final products. As silylated 5-hydroxymethyluracil **25** had limited solubility in DCM, the preferred medium for glycosylation reactions, its glycosylations with **1n**/**1n′** were performed following the one-pot silylation/glycosylation procedure to yield *N*-glycosides **26** and **26′** almost quantitatively. Desilylation was followed by O-glycosylation with **1b** to provide **27** (78%, 2 steps from **26**) and **27′** (75%, 2 steps from **26′**). Compounds **27** and **27′** were then separately subjected to photocatalyzed deoxygenation, delivering fully protected dJ **28** (80%) and its analog **28′** (81%). Finally, saponification of all Bzs under basic conditions converted **28**/**28′** to dJ **24** (99%) and its 3′-deoxy analog **24′** (95%), respectively, free of by-products originating from decomposition[54]. Thus, following this approach, both dJ **24** and its analog **24′** could be obtained through 7-step LLSs in 30% and 28% overall yield, respectively. It is noteworthy that the timing of the deoxygenation step is crucial for the success of this divergent approach. If the deoxygenation step was carried out before the *O*-glycosylation step, partial cleavage of the *N*-glycosidic linkage was observed.

In summary, thanks to the favorable activating effect on the leaving group and appropriate stabilizing effect on the key catalyst intermediate, the tert-butyl substituent vitalized a type of o-alkynylphenylthioglycosides donors, the BEPT donors. The reaction mechanism of the BEPT donor with nucleobase was investigated by model/control reactions, NMR experiments, and DFT calculations, justifying the BEPTs as viable donors in nucleoside preparation. With the stable glycosyl BEPTs as donors, a protocol for nucleosides synthesis has been established, through which direct (without resorting to nucleobase activation/sylylation), swift (the reaction time could be reduced to 10 min), and highly efficient synthesis of nucleosides has been achieved via either the PG or the solvent procedures under mild conditions (0.02–0.2 equivalents of Au(I) catalyst). Taking advantage of the stereo-controlling and deoxygenating capabilities of the DHIN group, stereoselective 2-step synthesis of 2′-deoxy nucleosides was achieved through the BEPT protocol. The beneficial effect of the HFIP was disclosed both in PG and in solvent procedures, not only dramatically speeding up the reaction rate but also allowing free uracil derivatives as viable acceptors, which dramatically streamlines the chemical synthesis of nucleosides. The underlying mechanism responsible for the rapid and regioselective synthesis of uracil-type nucleosides via the solvent procedure was elucidated by DFT calculations and NMR experiments, confirming the formation of favorable H-bond systems. Moreover, direct comparison of the BEPT protocol with the other two catalytic protocols, including the ABz and EGC protocols, was made. Other *N*-nucleophiles such as carbazoles, pyrazoles, indazoles, 1,3,4-triazoles, asparagine, and asparagine-embed peptides were included as viable acceptors for the BEPT protocol, and scalable synthesis of nucleosides through the BEPT protocol was achieved, leading to gram-scale preparation of chloro-substituted nucleoside and cladribine, the two highly biologically relevant nucleosides, all of which underscore the advantages of the BEPT protocol over the existing protocols. To further evaluate the practicability of the BEPT protocol, syntheses of augustmycin A (11 LLS, 15%), dJ (25%, 5 LLS, and 30%, 7 LLS), and dJ 3′-deoxy analog (28%, 7 LLS), the highly bioactive but synthetically challenging nucleosides, were accomplished. As such, the establishment of the BEPT protocol dramatically facilitates the access of nucleoside compounds, thereby considerably accelerating the process of nucleoside drug development[55].

Additionally, during the synthesis of dJ and its analog, the glycosyl BEPT donor also had impressive performance in O-glycosidic linkages construction. Thus, the wide application of the BEPT protocol in *O*-glycosides synthesis, especially the challenging β-mannosides[56] as well as the α-sialosides[57], could definitely be expected. The related studies are underway in our lab, and the results will be reported in the near future.

Methods

General procedure for the N-glycosylation of purines or pyrimidines with BEPT donors

General Procedure A. A suspension of donor (1.2 equiv, 30 or 60 mM), acceptor (1.0 equiv), and freshly activated 5A molecular sieves (4 g/mmol) in dry CH_2Cl_2 was stirred at room temperature for 15 min under N_2 atmosphere, then PPh_3AuNTf_2 (0.02–0.2 equiv) was added at the same temperature. The resulting reaction mixture was stirred at the same temperature until TLC showed that the coupling had reached completion. Then the mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by column chromatography on silica gel to provide the corresponding product.

General Procedure B. A suspension of donor (1.2 eq, 40 mM), acceptor (1.0 equiv), and freshly activated 5A MS (4 g/mmol) in a mixed solvent of dry CH_2Cl_2 and HFIP (v/v = 4:1) was stirred at room temperature for 15 min under N_2 atmosphere, then PPh_3AuNTf_2 (0.02 or 0.04 equiv) was added at the same temperature. The resulting reaction mixture was stirred at the same temperature until TLC showed that the coupling had reached completion. Then the mixture was filtered, and the filtrate was concentrated. The resulting residue was purified by column chromatography on silica gel to provide the corresponding product.

General Procedure C. A suspension of donor (1.2 equiv, 30 mM), acceptor (1.0 equiv), and freshly activated 4A MS (4 g/mmol) in dry CH_2Cl_2 was stirred at room temperature for 15 min under N_2 atmosphere, then PPh_3AuNTf_2 (0.2 equiv) was added. The resulting reaction mixture was stirred at the same temperature for 4 h. Then the reaction mixture was filtered, and the filtrate was concentrated to yield the crude product, which was purified by column chromatography on silica gel to provide the corresponding product.

General Procedure D. To a sealed tube, donor (1.0 equiv), acceptor (2 equiv, 50 mM), CH_2Cl_2, and BSTFA (4 equiv) were added successively at room temperature under N_2 atmosphere. The mixture was stirred at 80 °C until it became clear (about 8 h). The reaction mixture was then gradually cooled down to room temperature, to which 5A MS (4 g/mmol) and PPh_3AuNTf_2 (0.02–0.2 equiv) were added successively. The resulting mixture was stirred at the same temperature until TLC showed the completion of the reaction. Filtration and concentration under reduced pressure afforded a residue which was purified by column chromatography on silica gel to provide the corresponding product.

General Procedure E. A suspension of donor (1.0 equiv, 20 or 40 mM), acceptor (2.0 equiv), and freshly activated 5A MS (4 g/mmol) in a mixed solvent of dry CH_2Cl_2 and HFIP (v/v = 4:1) was stirred for 15 min at room temperature under N_2 atmosphere, then PPh_3AuNTf_2 (0.2 equiv) was added at the same temperature. The resulting reaction mixture was stirred at the same temperature until TLC showed that the coupling had reached completion. Filtration was followed by concentration under reduced pressure to provide the crude product, which was further purified by column chromatography on silica gel to provide the corresponding product.

Data availability

All the relevant data are available from the corresponding author on request and/or are included within the manuscript and supplementary materials. Source data are provided with this paper. The X-ray crystallographic coordinates for structures reported in this study have been deposited at the Cambridge Crystallographic Data Centre (CCDC), under deposition numbers 2414077 and 2401831. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Source data are provided with this paper.

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Author contributions

J.-S.S. designed the project. H.L., M.-Y.W., T.M., X.-X.L., J.-J.G., M.-Z.T., Y.-H.T., and D.-Y.L. performed the synthetic and NMR experiments. H.X., Y.Q., and X.S. performed the DFT calculations. H.L. and J.-S.S. compiled and analyzed the data, and wrote/revised the main test and Supplementary Information parts. H.L., J.-X.L., and J.-S.S. supervised the project.

Competing interests

The authors declare no competing interests.

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