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Phosphite mediated asymmetric N to C migration for the synthesis of chiral heterocycles from primary amines†

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A phosphite mediated stereoretentive C–H alkylation of *N*-alkylpyridinium salts derived from chiral primary amines was achieved. The reaction proceeds through the activation of the *N*-alkylpyridinium salt substrate with a nucleophilic phosphite catalyst, followed by a base mediated [1,2] aza-Wittig rearrangement and subsequent catalyst dissociation for an overall N to C-2 alkyl migration. The scope and degree of stereoretention were studied, and both experimental and theoretical investigations were performed to support an unprecedented aza-Wittig rearrangement–rearomatization sequence. A catalytic enantioselective version starting with racemic starting material and chiral phosphite catalyst was also established following our understanding of the stereoretentive process. This method provides efficient access to tertiary and quaternary stereogenic centers in pyridine systems, which are prevalent in drugs, bioactive natural products, chiral ligands, and catalysts.

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Introduction

The recent focus on sustainable chemistry has encouraged chemists to develop the direct and diverse functionalization of abundant and renewable chemicals.¹ In this context, primary alkyl amines have emerged as an inexpensive, stable, and abundant source for the generation of reactive intermediates. In a recent application of its use as an alkylating agent,² the Watson group in 2017 developed an elegant nickel catalysed method to generate alkyl radicals from stable Katritzky pyridinium salts of primary amines for their coupling with aryl-boronic acids.³ In the same year, the Glorius group reported an iridium based photoredox catalysed protocol for alkyl radical generation and its coupling with heteroaromatic compounds.⁴ Since then, this approach has become a focus of intensive study *via* new and elegant deaminative protocols with diverse reaction partners under photoredox and dual catalysis or with redox-active coupling partners (Fig. 1a).^{5,6} These deaminative processes to alkyl radicals lead to racemic products from both achiral and enantioenriched amines. Additionally, the C–N bond cleavage processes generate triphenylpyridine as a part of the waste stream.

We reasoned that the unique reactivity of pyridinium salts could be exploited to generate enantioenriched products that retain the pyridine ring system. The synthetic utility of our approach lies in the various simple methods for generating

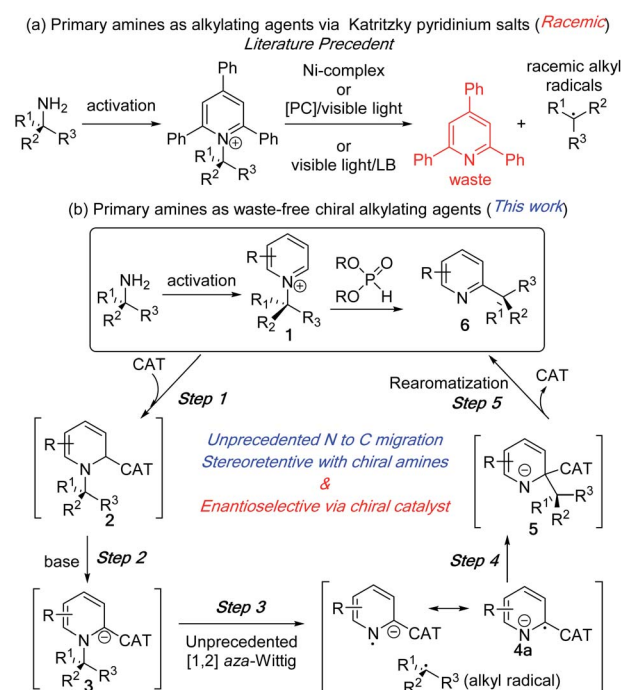


Fig. 1 Primary amines as alkylating reagent. (a) Literature precedents. (b) Proposed N to C dissociative alkyl migration.

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alkylpyridinium salts other than Katritzky salts (**1**) from amines.⁷ Despite the prevalence of chiral alkyl pyridines (**6**) and the corresponding saturated heterocycles in numerous pharmaceutical drugs and biologically active compounds,⁸ their enantioselective synthesis *via* catalytic methods remains a challenge.^{9–12} In this communication, we report an intramolecular alkylation process with chirality transfer to synthesize chiral pyridines from enantioenriched pyridinium salts without the loss of pyridines as waste (Fig. 1b). We also report a catalytic enantioselective version of this unprecedented N to C alkyl migration from racemic *N*-alkylpyridinium salt.

The reaction development strategy is based on our experience in various selective molecular rearrangements and radical reactions.^{11e,13} We envisioned that a suitable catalyst adduct (**2**), upon deprotonation could form a reactive carbanion (**3**) and subsequent stable radical anion (**4a**) to reduce the activation energy to effect an [1,2] *aza*-Wittig rearrangement (**3** to **5**, Fig. 1b). To the best of our knowledge, the anionic [1,2] *aza*-rearrangement is not known, presumably due to its high activation energy requirement.¹⁴ The [1,2] alkyl migration (**5**) intermediate would undergo a facile catalyst dissociation to waste-free intramolecular C–H alkylation product (**6**). This subsequent rearomatization exothermic step after the *aza*-Wittig should favour the overall thermodynamics. Although the C–N bond breaks during the rearrangement, the stereochemical outcome of this intramolecular process would be intriguing.¹⁵ A

highly stereoretentive migration or a chiral catalyst controlled stereoselective recombination of radical pair could provide us with multiple pathways to control the stereoselectivity.

To explore the feasibility of alkyl migration, racemic (*S*)-1-phenylethylamine salt of isoquinoline (**1a**) was selected as the substrate. A variety of catalysts were screened based on their nucleophilicity, and subsequent anion and radical stabilization ability (Table 1).^{13,16} NHC catalysts, DBU, and thiophenol were unsuccessful with different bases (entries 1–4). But, to our delight, the addition of stoichiometric diethylphosphite anion at room temperature, followed by treatment with 2.5 equivalents of LiHMDS at 0 °C led to 58% of the migration product **6a** (Table 1, entry 5).¹⁷ With a suitable catalyst in hand, we performed the reaction with enantioenriched **1a** to explore the stereochemical outcome. The chiral pyridinium salt ((*S*)-**1a**) was synthesized from commercially available chiral (*S*)-1-phenylethylamine.^{7b} The migration in THF at 0 °C with (*S*)-**1a** led to an encouraging 86% enantiospecificity (es) with retention of the configuration (entry 6).⁹ Next, we optimize our stereoretentive method, starting with screening the role of solvent. MTBE instead of THF led to 88% es, while toluene led to 91% es (entries 7 and 8). Cyclohexane as solvent did not improve the stereoretention (90% es, entry 9), but DCM as solvent led to 96% es (entry 10). The counter cation of the HMDS base also plays a significant role, with sodium being more effective than lithium (entry 11).¹⁸ Other phosphites were tested next, which

Table 1 Optimization study for phosphite mediated N to C migration^a

Entry	C (mol%)	T (°C)	Base-1	Base-2	Solvent	6a , yield (%)	6a , % ee (es)
1	C1 (50)	60	Cs ₂ CO ₃	Cs ₂ CO ₃	THF	ND	—
2	C2 (50)	60	Cs ₂ CO ₃	Cs ₂ CO ₃	THF	ND	—
3	C3 (50)	60	Cs ₂ CO ₃	Cs ₂ CO ₃	THF	ND	—
4	C4 (100)	25	K ₂ CO ₃	LiHMDS	THF	ND	—
5	C5 (100)	0	K ₂ CO ₃	LiHMDS	THF	58	—
6	C5 (100)	0	K ₂ CO ₃	LiHMDS	THF	63	69 (86)
7	C5 (100)	0	K ₂ CO ₃	LiHMDS	MTBE	61	73 (88)
8	C5 (100)	0	K ₂ CO ₃	LiHMDS	Toluene	64	80 (91)
9	C5 (100)	0	K ₂ CO ₃	LiHMDS	Cyclohexane	47	78 (90)
10	C5 (100)	0	K ₂ CO ₃	LiHMDS	DCM	67	90 (96)
11	C5 (100)	0	K ₂ CO ₃	NaHMDS	DCM	70	90 (96)
12	C6 (100)	0	K ₂ CO ₃	NaHMDS	DCM	66	88 (95)
13	C7 (100)	0	K ₂ CO ₃	NaHMDS	DCM	55	85 (93)
14	C8 (100)	0	K ₂ CO ₃	NaHMDS	DCM	26	59 (80)
15	C5 (100)	−20	K ₂ CO ₃	NaHMDS	DCM	72	91 (96)
16	C5 (100)	−40	K ₂ CO ₃	NaHMDS	DCM	69	91 (96)
17	C5 (100)	−60	K ₂ CO ₃	NaHMDS	DCM	70	91 (96)
18 ^b	C5 (20)	−60	K ₂ CO ₃	NaHMDS	DCM	67	91 (96)
19 ^c	C5 (100)	−20	K ₂ CO ₃	NaHMDS	DCM	72	92 (97)
20 ^d	C5 (100)	−20	K ₂ CO ₃	NaHMDS	DCM	70	92 (97)

^a Reactions were carried out with 0.3 mmol **1a**, 4 ml solvent, and 1 M THF solution of MHMDS base. ^b With catalytic (20 mol%) dimethylphosphite diethylphosphite catalyst (see ESI for procedure). ^c With 2 M NaHMDS in THF. ^d 1 mmol scale.

reveals better results with smaller alkoxy groups (entries 12–14). Finally, the optimal reaction temperature was determined to be $-20\text{ }^{\circ}\text{C}$ (entries 15–17). Although the racemic diethylphosphite can be used in catalytic amounts under strict deoxygenated conditions at lower temperature (entry 18), we utilized stoichiometric amounts of the phosphites to simplify the operation to obtain the product at a shorter reaction time, since diethylphosphite is non-toxic and cheaper than the reaction solvents. Since THF is detrimental to the stereoretention (entries 6 vs. 9), we performed the reaction with 2 M THF solution of NaHMDS instead of 1 M, which improved the es to 97% (entry 19), leading to substituted isoquinoline (*S*)-**6a** in 72% yield and 92% ee from

enantioenriched (98% ee) (*S*)-1-phenylethylamine salt (**1a**).¹⁹ The optimized reaction works well on 1 mmol scale, with no change in stereoretention and comparable yield (entry 20).

With optimized reaction conditions in hand, we tested the generality of our stereoretentive method for both chiral amines²⁰ and pyridine derivatives. First, we explored the scope and efficiencies of different chiral amines with isoquinoline (Table 2). Gratifyingly, the enantiomer of **1a** (*ent*-**1a**) led to an efficient synthesis of *ent*-**6a**. Alkyl groups other than methyl at the migrating carbon such as ethyl (**6b**), cyclopropyl (**6c**), fused cyclopentyl (**6d**), and cyclohexyl (**6e**) were all resulted in good yields with almost quantitative chirality transfer. These

Table 2 Isoquinoline substrate scope for stereoretentive alkyl migration^a

			<div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p style="text-align: center;">Methylberberines</p> <p style="text-align: center;">R¹ = OMe, R² = H R¹ = H, R² = OMe</p> </div>		

^a Conditions: **1** (0.3 mmol) was dissolved in 3 ml DCM and added to diethylphosphite (0.3 mmol) and K₂CO₃ (0.75 mmol) in 1 ml DCM at 25 °C and stirred for 24 h. Then the reaction mixture was cooled to $-20\text{ }^{\circ}\text{C}$ and NaHMDS (2.5 equiv., 2 M in THF) was added and stirred for 12 h.



Quantum chemical calculations (DFT, details in ESI†) were performed to gain insight into the crucial C–N bond breaking (step 3, Fig. 1b) and C–C bond forming (step 4, Fig. 1b) steps of our proposed phosphite catalysed *aza*-Wittig, and subsequent

Reaction scheme for the synthesis of chiral (halo)phenylamines (6a-f) and (halo)phenylamines (7a-d) via asymmetric nucleophilic aromatic substitution (S_NAr).

Reaction Conditions:

- DEHP:K₂CO₃ (1:2.5), DCM, 25 °C, 24 h
- NaHMDS (2.5 equiv), -20 °C, 12 h

Starting Material 1: A chiral pyridine derivative with substituents R¹, R², and R³, and a BF₄⁻ counterion.

Products:

- 6 (7-20%):** A chiral pyridine derivative with substituents R¹, R², and R³.
- 7 (7-20%):** A chiral pyridine derivative with substituents R¹, R², and R³.

Reaction Results:

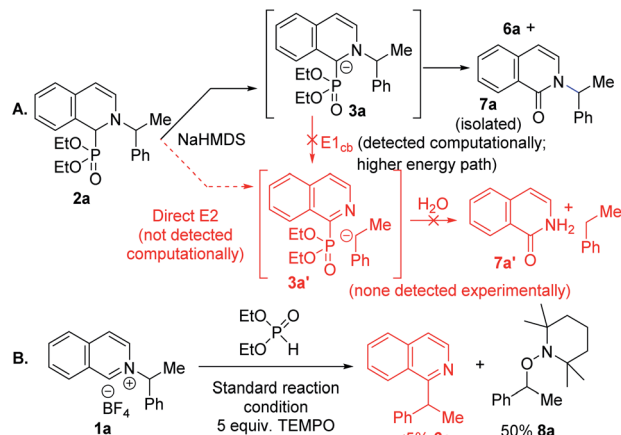
Starting Material	Product	Yield (%)	Enantiomeric Excess (ee) (%)
1 (Me, Ph, Me)	6a	40	91
1 (Me, Ph, Me)	7a	20	81
1 (Me, Ph, Me)	6b	45	93
1 (Me, Ph, Me)	7b	8	84
1 (Me, Ph, Me)	6c	43	87
1 (Me, Ph, Me)	7c	10	72
1 (Me, Ph, Me)	6d	43	93
1 (Me, Ph, Me)	7d	7	82
1 (Me, Ph, Me)	6e	53	80

Notes:

- Reaction 6a-f: (Halo)phenylamines (6a-f) are formed with high enantiomeric excess (ee) and yield.
- Reaction 7a-d: (Halo)phenylamines (7a-d) are formed with lower enantiomeric excess (ee) and yield.
- Reaction 6e: (Halo)phenylamine (6e) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6f: (Halo)phenylamine (6f) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6g: (Halo)phenylamine (6g) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6h: (Halo)phenylamine (6h) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6i: (Halo)phenylamine (6i) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6j: (Halo)phenylamine (6j) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6k: (Halo)phenylamine (6k) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6l: (Halo)phenylamine (6l) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6m: (Halo)phenylamine (6m) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6n: (Halo)phenylamine (6n) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6o: (Halo)phenylamine (6o) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6p: (Halo)phenylamine (6p) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6q: (Halo)phenylamine (6q) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6r: (Halo)phenylamine (6r) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6s: (Halo)phenylamine (6s) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6t: (Halo)phenylamine (6t) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6u: (Halo)phenylamine (6u) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6v: (Halo)phenylamine (6v) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6w: (Halo)phenylamine (6w) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6x: (Halo)phenylamine (6x) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6y: (Halo)phenylamine (6y) is formed with 80% ee (91% es) and 53% yield.
- Reaction 6z: (Halo)phenylamine (6z) is formed with 80% ee (91% es) and 53% yield.

Experimental mechanistic studies were carried out to support or discredit the alternative paths identified in the computational studies (Scheme 1). We noticed that in the presence of traces of oxygen, the corresponding pyridone side product formed with the C–N bond intact under the N to C

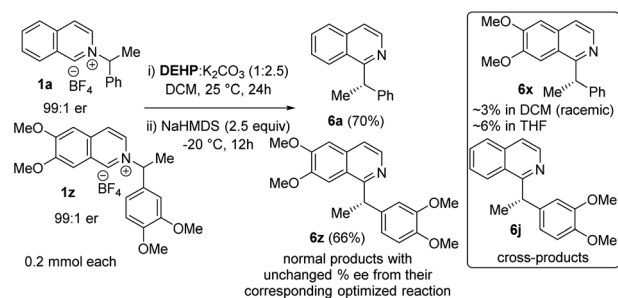
Substrate	DFT methods	Homo	Hetero	Homo-hetero
1a	PBE/def-TZVP	-0.8	+1.6	-2.4
	B3LYP/def2-TZVPP	-5.0	-1.4	-3.6
	B3LYP/6-31+G**	-16.9	-10.5	-6.4
	M06-2X/6-31+G**	+1.8	+7.2	-5.4
	M06-2X/6-311+G**	+4.1	+8.0	-3.9
1u	PBE/def-TZVP	-6.9	-1.2	-5.7
	B3LYP/def2-TZVPP	-11.1	-3.9	-7.2



Scheme 1 Mechanistic studies. (A) Homolytic vs. heterolytic paths *via* intermediate trapping. (B) Radical trap with TEMPO.

migration protocol (Scheme 1a). This result is suggestive of a common carbanionic intermediate **3a** for its competing Nef oxidation *versus* alkyl migration.^{21a} An E1_{cb} pathway would lead to C–N bond cleaved intermediate **3a'**, or its hydrolyzed product **7a'**, which were not detected. A direct base mediated E2 pathway to **3a'** could also be a possibility, but was not detected computationally. To further distinguish between heterolytic E1_{cb}/E2 and homolytic radical pair paths, a radical trapping experiment was conducted with TEMPO. The addition of five equivalents of TEMPO led to a complete shut down of the alkyl migration with 50% TEMPO trapped alkyl product formation (Scheme 1b). No alkyl migration product under excess radical trap reagent along with trapped alkyl product supports a radical pair mechanism.²⁷

Next, we examined the source of high stereoretention for this dissociative alkyl migration (Scheme 2). For [1,2] *oxa*-Wittig rearrangements, the commonly accepted explanation for stereoretention at the migrating centre is that the radical pair formation and recombination occurs within the solvent cage.¹⁵ This solvent-caged radical pair recombination is faster than racemization through solvent-cage escape and recapture. On the other hand, out-of-plane rotation within the solvent cage can also lead to racemization.²⁸ To gain insight, we conducted a crossover experiment with **1a** and **1z** in DCM and THF. The cross-products formations in DCM are ~2–3%, which supports predominantly solvent-caged radical recombination. In THF,

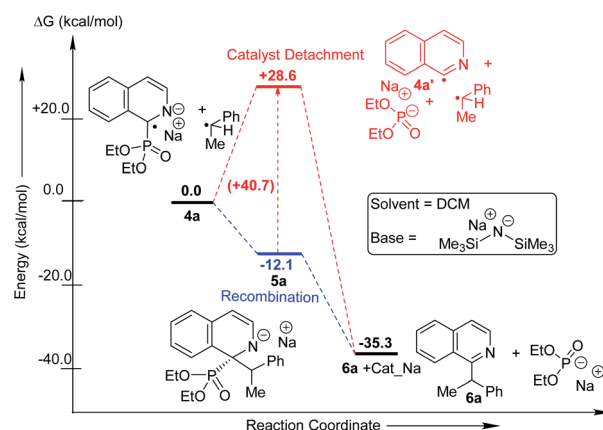


Scheme 2 Crossover experiment & stereoretention.

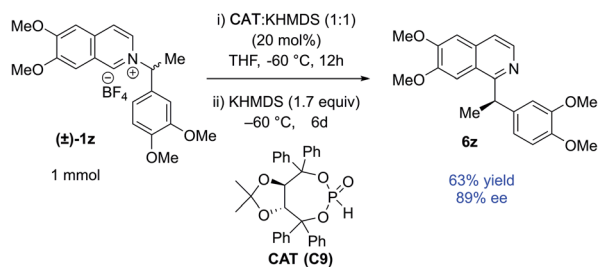
the cross-products are ~4–6%, which is consistent with less stereoretention in that solvent. The chiral HPLC analysis of cross-products showed that those were rendered almost racemic, supporting solvent cage escape as one possible pathway for racemization. The normal products, which now have less 'solvent-cage escape and recapture' possibility in the crossover experiment, did not result in significantly higher stereoretention. Therefore an out-of-plane rotation within the solvent cage cannot be ruled out.

We performed computational studies for radical pair recombination in order to determine the exact juncture of catalyst detachment (step 4, Fig. 1b; Scheme 3). The catalyst detachment from radical **4a** to **4a'**, prior to its recombination with alkyl radical, signifies no catalyst control on the subsequent C–C bond formation. Although we predict radical **4a** formation from anionic intermediate **3a** would be stabilized by captodative effect and extended delocalization, the formation of **4a'** might be feasible owing to the rearomatization of the heterocycle. The calculations reveal that this is highly unlikely, since the ΔG for the corresponding imine radical (**4a'**) formation is endothermic by 28.6 kcal mol⁻¹. The loss of conjugation and captodative stability seems to outweigh the rearomatization in **4a'**. The recombination of the catalyst attached **4a** at C-2 with the alkyl radical could, therefore, be influenced by the catalyst. The subsequent catalyst release from **5a** leading to the rearomatized final product (**6a**) is found to be highly exothermic (23.1 kcal mol⁻¹), which makes the overall transformation favourable.

The catalyst involvement in the C–C bond formation and the possibility of racemization *via* dissociative path led us to speculate if a chiral phosphite catalyst could induce enantioselective transformation starting with racemic pyridinium salts. During reaction optimization, we observed variable degrees of racemization with different catalysts (Table 1). The significant drop in stereoretention with a bulky *tert*-butyl phosphite (80 vs. 96% es, Table 1, entries 12 & 14) could be due to its slower recombination, with racemization paths in play. Therefore, a bigger chiral phosphite catalyst could also slow the recombination for the racemic alkyl radical to allow its rotation to catalyst controlled



Scheme 3 Computed C–C bond formation and subsequent rearomatization energy profile.



Scheme 4 Chiral phosphite catalyzed enantioselective N to C migration.

enantioselection. Since the reaction medium influences the stereoretention (Table 1, entries 7–10), solvents with high racemization might also provide time for the alkyl radical to rotate for the enantioselection. We chose racemic **1z** as a test substrate, since it can be converted to natural products, and its stereoretentive migration generated the product in a modest 83% ee (92% es, Table 2). To our delight, 20 mol% TADDOL-phosphite catalyst (**C9**) generates chiral **6z** with 89% ee in THF (Scheme 4, see ESI† for details). This result represents a proof-of-concept for the chiral phosphite catalyzed enantioselective N to C migration of racemic pyridinium salts.

In conclusion, a phosphite mediated stereoretentive C–H alkylation of *N*-alkylpyridinium salt was developed. Chiral alkylpyridines were obtained from the corresponding chiral amines with a broad range of functional groups. An all-carbon quaternary alkyl group also migrated efficiently. The mechanistic experiments suggest a phosphite catalyzed bis-radical [1,2] *aza*-Wittig followed by rearomatization *via* catalyst release for product formation. Exploring the source of stereoretention and a variable degree of racemization led us to establish a chiral phosphite catalyzed enantioselective version with racemic alkylpyridinium salt. The dissociative reaction path presents us with the possibility of [1,*n*] alkyl migrations other than the present [1,2] in and around pyridines, which we are exploring currently. Synthesis of natural and bioactive compounds from the chiral alkylpyridines is also under development.

Data availability

The complete data supporting this article have been uploaded as part of the supplementary material.

Author contributions

S. R. and A. B. performed the experiments and developed the method. S. R. D. performed the DFT calculation in consultation with K. V. and P. M.; Md N. A. finalized the data. P. M. directed the project and wrote the manuscript with the feedback from other authors.

Conflicts of interest

There are no conflicts of interest to declare.

Acknowledgements

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