Volume 12
Number 26
14 July 2021
Pages 8933–9248

Chemical Science

rsc.li/chemical-science

ISSN 2041-6539

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE
Pradip Maity *et al.*
Phosphite mediated asymmetric N to C migration for the synthesis of chiral heterocycles from primary amines

Chemical Science

ROYAL SOCIETY OF CHEMISTRY

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2021, **12**, 8996

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 2nd March 2021
Accepted 27th May 2021

DOI: 10.1039/d1sc01217g

rsc.li/chemical-science

Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

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

Soniya Rani,[ab] Soumya Ranjan Dash,[bc] Asish Bera,[ab] Md Nirshad Alam,[ab] Kumar Vanka[bc] and Pradip Maity*[a]

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.

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 arylboronic 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

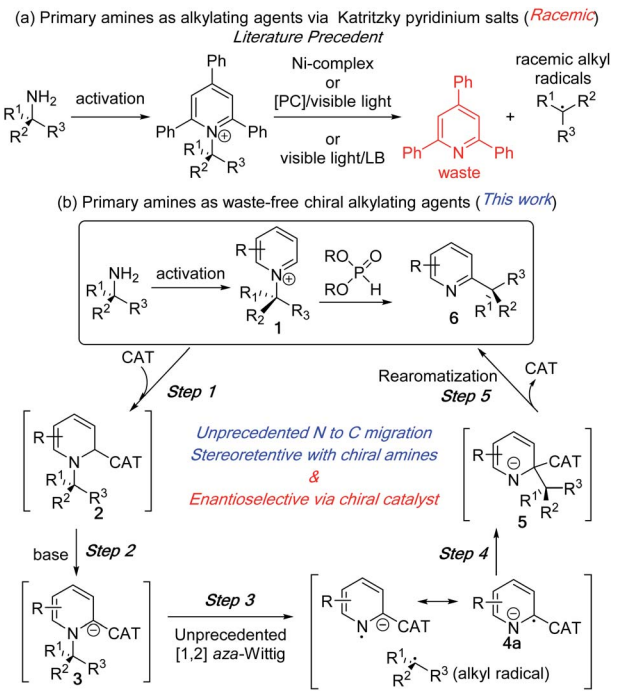


Fig. 1 Primary amines as alkylating reagent. (a) Literature precedents. (b) Proposed N to C dissociative alkyl migration.

[a]*Organic Chemistry Division, CSIR-National Chemical Laboratory, Pune-411008, India. E-mail: p.maity@ncl.res.in*

[b]*Academy of Scientific and Innovative Research (AcSIR), Ghaziabad-201002, India*

[c]*Physical and Material Chemistry Division, CSIR-National Chemical Laboratory, Pune 411008, India*

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1sc01217g

© 2021 The Author(s). Published by the Royal Society of Chemistry

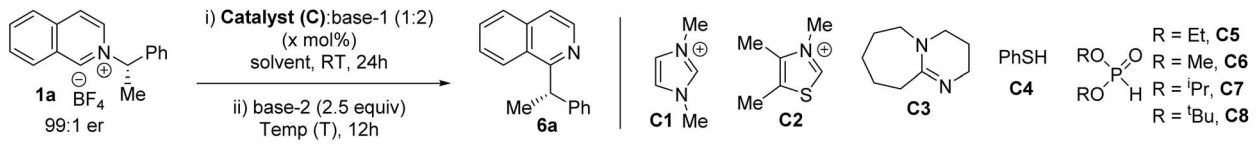
Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

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).[9j] 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_2CO_3	Cs_2CO_3	THF	ND	—
2	**C2** (50)	60	Cs_2CO_3	Cs_2CO_3	THF	ND	—
3	**C3** (50)	60	Cs_2CO_3	Cs_2CO_3	THF	ND	—
4	**C4** (100)	25	K_2CO_3	LiHMDS	THF	ND	—
5	**C5** (100)	0	K_2CO_3	LiHMDS	THF	58	—
6	**C5** (100)	0	K_2CO_3	LiHMDS	THF	63	69 (86)
7	**C5** (100)	0	K_2CO_3	LiHMDS	MTBE	61	73 (88)
8	**C5** (100)	0	K_2CO_3	LiHMDS	Toluene	64	80 (91)
9	**C5** (100)	0	K_2CO_3	LiHMDS	Cyclohexane	47	78 (90)
10	**C5** (100)	0	K_2CO_3	LiHMDS	DCM	67	90 (96)
11	**C5** (100)	0	K_2CO_3	NaHMDS	DCM	70	90 (96)
12	**C6** (100)	0	K_2CO_3	NaHMDS	DCM	66	88 (95)
13	**C7** (100)	0	K_2CO_3	NaHMDS	DCM	55	85 (93)
14	**C8** (100)	0	K_2CO_3	NaHMDS	DCM	26	59 (80)
15	**C5** (100)	−20	K_2CO_3	NaHMDS	DCM	72	91 (96)
16	**C5** (100)	−40	K_2CO_3	NaHMDS	DCM	69	91 (96)
17	**C5** (100)	−60	K_2CO_3	NaHMDS	DCM	70	91 (96)
18[b]	**C5** (20)	−60	K_2CO_3	NaHMDS	DCM	67	91 (96)
19[c]	**C5** (100)	−20	K_2CO_3	NaHMDS	DCM	72	92 (97)
20[d]	**C5** (100)	−20	K_2CO_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.

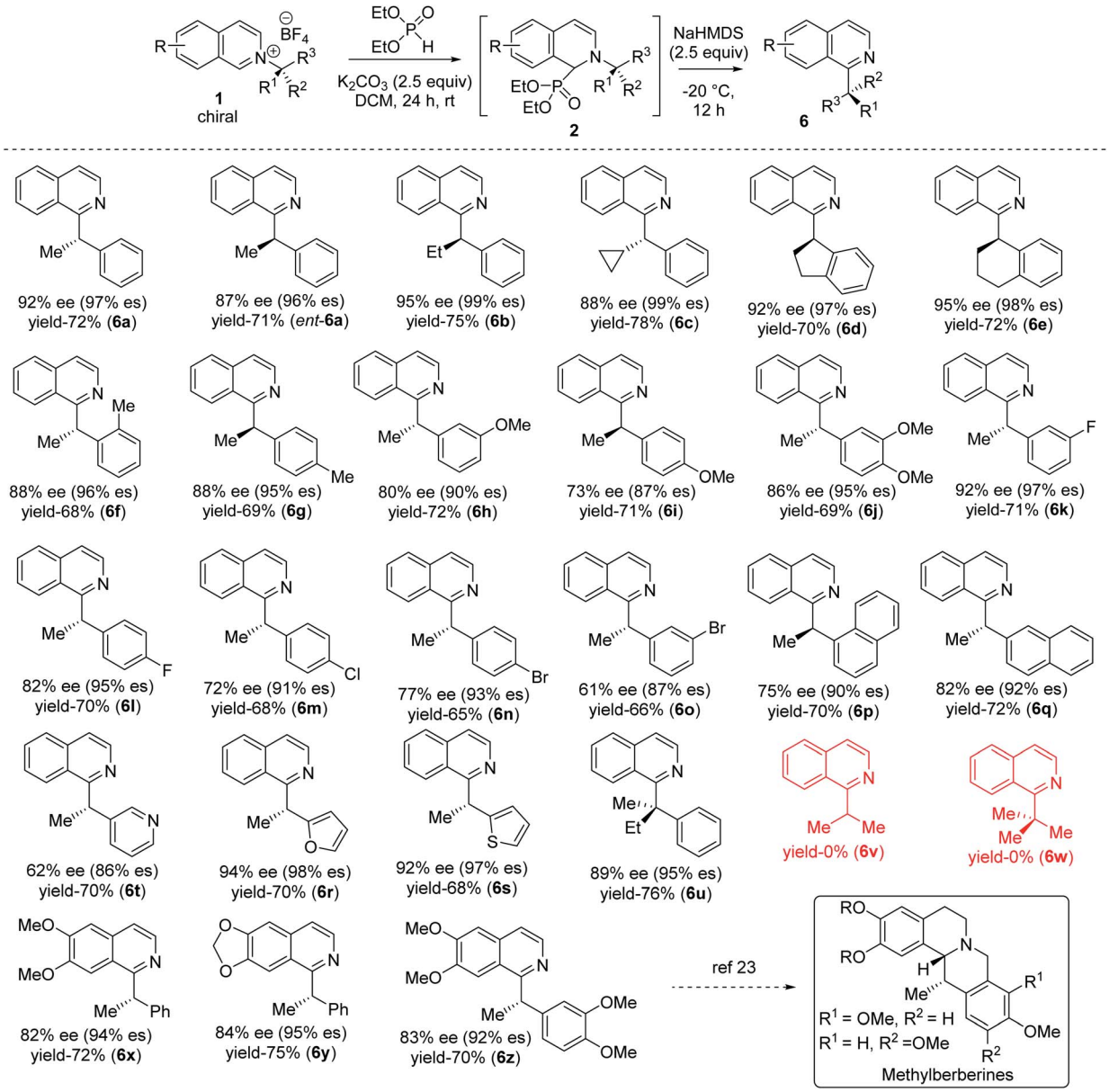
© 2021 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

reveals better results with smaller alkoxy groups (entries 12–14). Finally, the optimal reaction temperature was determined to be −20 °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 amines[20] 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]



[a] Conditions: **1** (0.3 mmol) was dissolved in 3 ml DCM and added to diethylphosphite (0.3 mmol) and K_2CO_3 (0.75 mmol) in 1 ml DCM at 25 °C and stirred for 24 h. Then the reaction mixture was cooled to −20 °C and NaHMDS (2.5 equiv., 2 M in THF) was added and stirred for 12 h.

© 2021 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

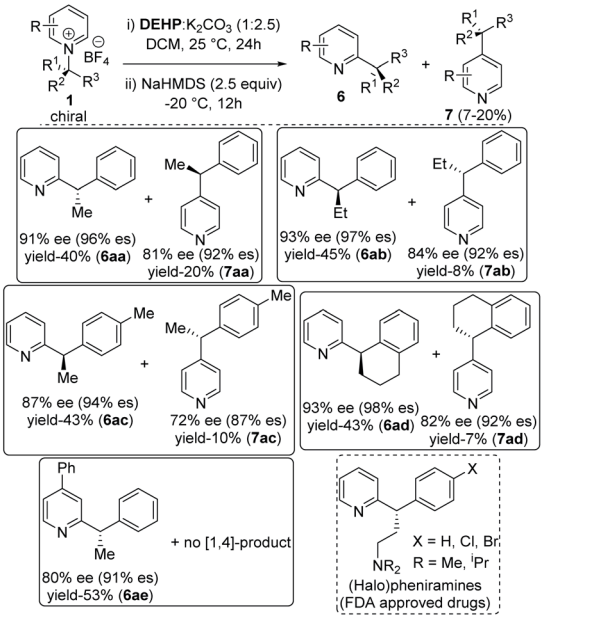
examples showed that the alkyl group at migrating carbon has very little influence on the reaction outcome. The α-cyclopropyl group at migrating carbon is significant with no ring-opening product was observed.[21] Next, we varied the aryl groups at the migrating carbon. Methyl at *ortho*- (**6f**) and *para*-position (**6g**) of the phenyl ring led to similar results, indicating a minimal steric effect on yield and enantiospecificity. Methoxy substitution at both C-3 (**6h**) and C-4 (**6i**) led to lower stereoretention (90 and 87%), whereas 3,4-dimethoxy substitution (**6j**) lead to 95% es. The yields are comparable to that of parent substrate for all methoxyaryl substrates. Halo substituents at C-3 and C-4 positions were well tolerated. Fluoro substituent at C-3 led to 97% es (**6k**), while C-4 fluro resulted in 95% es (**6l**). Both chloro and bromo substitution resulted in slightly lower chirality transfer (**6m**,**n**,**o**). α-Napthyl instead of phenyl formed product with 90% es (**6p**), and β-naphthyl yielded the corresponding products with 92% es (**6q**). Heteroaryl groups at the migrating center such as electron-rich 2-furan (**6r**) and 2-thiophene (**6s**) both migrated with excellent enantiospecificity (98 & 97% es), while electron-deficient 3-pyridine (**6t**) led to a moderate 86% es. Finally, we synthesized an isoquinolinium salt of quaternary chiral amine (**1u**). Under optimized reaction conditions, it rearranged successfully to the corresponding all carbon quaternary alkyl chiral products with better yield (76%) and very good 95% es (**6u**). Isoquinolinium salts of isopropyl (**6v**) and *tert*-butyl (**6w**) amine did not lead to the product which indicates (hetero) aryl stabilization on migrating alkyl radical is necessary.

A diverse range of substituted pyridines was subjected to the reaction condition to find the generality of our method with azaarenes. Electron rich bis-alkoxy groups on isoquinolines were tested first since the corresponding products could be easily converted to the numerous natural products of biological importance.[22] 4,5-Bis-alkoxyisoquinoline derivatives of (*S*)-1-phenylethylamine (**6x**, **6y**) resulted in 94 and 95% es with 72 and 75% yields respectively. With 4,5-dimethoxyisoquinoline and 3,4-dimethoxyphenylethylamine, the product **6z** is obtained in 70% yield with 92% es. **6z** and its reduced forms were utilized for the synthesis of various methylberberine alkaloids.[22a,c]

Finally, the alkyl migration protocol was tested on unsubstituted pyridine substrates, which are common pharmacophores in many approved pharmaceutical drugs.[7,23] Under standard reaction condition, the C-2 alkyl migrated products formed in moderate yields but with excellent enantiospecificity (Table 3). The stereoretention trend in alkyl migration runs parallel to that in isoquinoline substrates. For 4-unsubstituted pyridines, a minor [1,4] migrated side products 7 also formed with 4–7% lower enantiospecificities. Competitive [1,4] Wittig rearrangements from common radical pair intermediates are known in literature, with a single report by Maleczka Jr group describes stereoretention pattern similar to our findings.[24] With pyridinium substrates, either the same C-2 added catalyst or a C-4 added catalyst intermediate can undergo the [1,4] migration.

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

Table 3 Pyridine substrate scope for stereoretentive alkyl migration



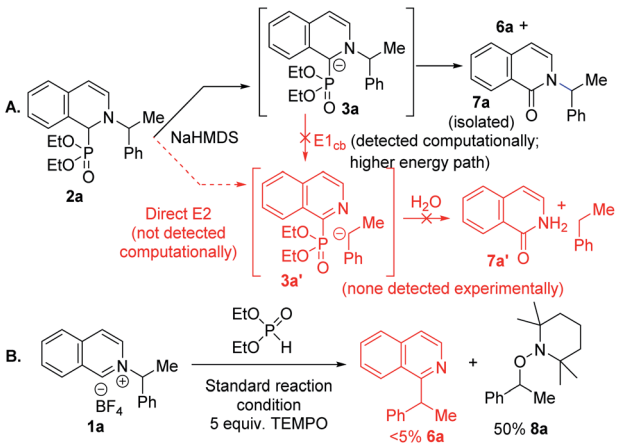
rearomatization protocol.[25] First, the C–N bond dissociation energy (BDE) was calculated at the PBE/def-TZVP level of theory. The ΔG for the homolytic C–N bond cleavage was calculated to be exothermic by 0.8 kcal mol^{-1}, supporting the stability of radical **4a** *via* the catalyst mediated captodative effect and extended conjugation.[13,16] An alternative heterolytic bond cleavage path with 2.4 kcal mol^{-1} higher energy *via* an E2 could also be identified during the calculations. To avoid any bias from the chosen DFT method, and since the difference between homolytic and heterolytic BDE was close, we used different levels of theory to compare the two possibilities.[26] In all cases, the homolytic dissociation was found to be favourable (Table 4). We also calculated homolytic and heterolytic dissociation for substrate **1u** with a quaternary migrating group, in which the homolytic cleavage is favoured by 5.7 kcal mol^{-1} (at the PBE/def-TZVP level of theory).

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

Table 4 Computed homolytic *vs.* heterolytic C–N bond dissociation energy (ΔG) in kcal mol^{-1}

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

Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



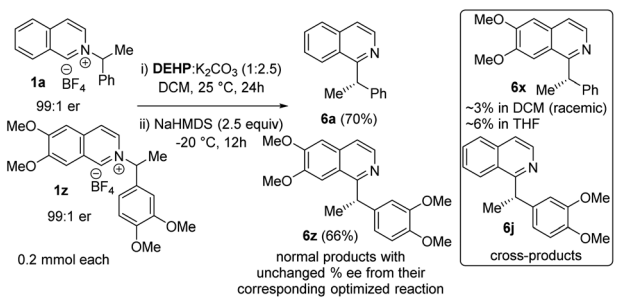
Scheme 1 Mechanistic studies. (A) Homolytic *vs.* heterolytic paths *via* intermediate trapping. (B) Radical trap with TEMPO.

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]

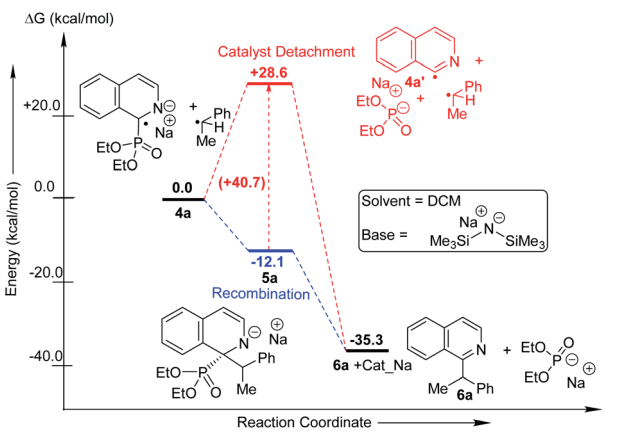
Next, we examined the source of high stereoretention for this dissociative alkyl migration (Scheme 2). For [1,2] *oxa*-Wittig rearrangements, the commonly accepted explanation for stereoretention at the migrating centre is that the radical pair formation and recombination occurs within the solvent cage.[15] 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, 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



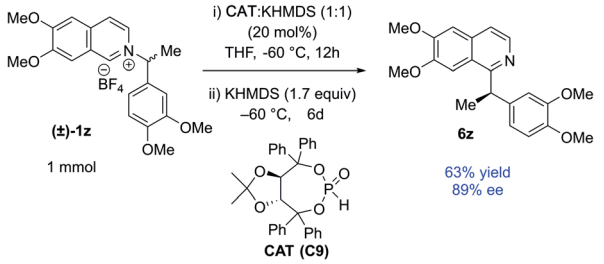
Scheme 2 Crossover experiment & stereoretention.



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

© 2021 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.



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

This research was supported by the SERB (EMR/2015/000711 and CRG/2019/001065). S. R. and A. B. thanks CSIR, and Md. N. A. thanks UGC for a fellowship. The support from central analytical facility, NCL is greatly acknowledged. We thank Dr S. H. Chikkali (NCL, Pune) for experimental help and Prof. U. K. Tambar (UTSW Medical Center, Dallas) for useful discussions and help in writing the manuscript. The support and the resources provided by 'PARAM Brahma Facility' under the National Supercomputing Mission, Government of India at the Indian Institute of Science Education and Research (IISER) Pune are gratefully acknowledged.

Notes and references

1 (*a*) V. Froidevaux, C. Negrell, S. Caillol, J.-P. Pascault and B. Boutevin, *Chem. Rev.*, 2016, **116**, 14181; (*b*) N. Burn, P. Hesemann and D. Esposito, *Chem. Sci.*, 2017, **8**, 4724; (*c*) M. Pelckmans, T. Renders, S. V. Vyver and B. F. Sels, *Green Chem.*, 2017, **19**, 5303.

2 (*a*) S. Crespi and M. Fagnoni, *Chem. Rev.*, 2020, **120**, 9790; (*b*) S. L. Rössler, B. J. Jelier, E. Magnier, G. Fagousset, E. M. Carreira and A. Togni, *Angew. Chem., Int. Ed.*, 2020, **59**, 9264; (*c*) D. Kong, P. J. Moon and R. J. Lundgren, *Nat. Catal.*, 2019, **2**, 473; (*d*) F.-S. He, S. Ye and J. Wu, *ACS Catal.*, 2019, **9**, 8943; (*e*) J. T. M. Correia, V. A. Fernandes, B. T. Matsuo, J. A. Delgado, W. C. de Souza and M. W. Paixao, *Chem. Commun.*, 2020, **56**, 503; (*f*) K. Ouyang, W. Hao, W.-X. Zhang and Z. Xi, *Chem. Rev.*, 2015, **115**, 12045.

3 C. H. Basch, J. Liao, J. Xu, J. J. Piane and M. P. Watson, *J. Am. Chem. Soc.*, 2017, **139**, 5313.

4 F. J. R. Klauck, M. J. James and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56**, 12336.

5 (*a*) J. Hu, G. Wang, S. Li and Z. Shi, *Angew. Chem., Int. Ed.*, 2018, **57**, 15227; (*b*) M. Ociepa, J. Turkowska and D. Gryko, *ACS Catal.*, 2018, **8**, 11362; (*c*) J. Liao, W. Guan, B. P. Boscoe, J. W. Tucker, J. W. Tomlin, M. R. Garnsey and M. P. Watson, *Org. Lett.*, 2018, **20**, 3030; (*d*) M.-M. Zhang and F. Liu, *Org. Chem. Front.*, 2018, **5**, 3443; (*e*) F. J. R. Klauck, H. Yoon, M. J. James, M. Lautens and F. Glorius, *ACS Catal.*, 2019, **9**, 236; (*f*) X. Jiang, M. M. Zhang, W. Xiong, L. Q. Lu and W. J. Xiao, *Angew. Chem., Int. Ed.*, 2019, **58**, 2402; (*g*) S. Plunkett, C. H. Basch, S. O. Santana and M. P. Watson, *J. Am. Chem. Soc.*, 2019, **141**, 2257; (*h*) H. Yue, C. Zhu, L. Shen, Q. Geng, K. J. Hock, T. Yuan, L. Cavallo and M. Rueping, *Chem. Sci.*, 2019, **10**, 4430; (*i*) S.-Z. Sun, C. Romano and R. Martin, *J. Am. Chem. Soc.*, 2019, **141**, 16197; (*j*) J. Yi, S. O. Badir, L. M. Kammer, M. Ribagorda and G. A. Molander, *Org. Lett.*, 2019, **21**, 3346; (*k*) S. Ni, C.-X. Li, Y. Mao, J. Han, Y. Wang, H. Yan and Y. Pan, *Sci. Adv.*, 2019, **5**, eaaw9516; (*l*) M. E. Hoerner, K. M. Baker, C. H. Basch, E. M. Bampo and M. P. Watson, *Org. Lett.*, 2019, **21**, 7356; (*m*) Z.-K. Yang, N.-X. Xu, C. Wang and M. Uchiyama, *Chem.–Eur. J.*, 2019, **25**, 5433; (*n*) Z.-F. Zhu, J.-L. Tu and F. Liu, *Chem. Commun.*, 2019, **55**,

Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM. This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

11478; (*o*) F. T. Pulikottil, R. Pilli, R. V. Suku and R. Rasappan, *Org. Lett.*, 2020, **22**, 2902; (*p*) C.-G. Yu and Y. Matsuo, *Org. Lett.*, 2020, **22**, 950; (*q*) J. Wang, M. E. Hoerner, M. P. Watson and D. J. Weix, *Angew. Chem., Int. Ed.*, 2020, **59**, 13484.

6 (*a*) J. Wu, L. He and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2018, **140**, 10700; (*b*) F. Sandfort, F. Strieth-Kalthoff, F. J. R. Klauck, M. J. James and F. Glorius, *Chem.–Eur. J.*, 2018, **24**, 17210; (*c*) J. Wu, P. S. Grant, X. Li, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2019, **58**, 5697; (*d*) M. Yang, T. Cao, T. Xu and S. Liao, *Org. Lett.*, 2019, **21**, 8673; (*e*) J. Hu, B. Cheng, X. Yang and T.-P. Loh, *Adv. Synth. Catal.*, 2019, **361**, 4902; (*f*) M. J. James, F. Strieth-Kalthoff, F. Sandfort, F. J. R. Klauck, F. Wagener and F. Glorius, *Chem.–Eur. J.*, 2019, **25**, 8240; (*g*) Q. Xia, Y. Li, X. Wang, P. Dai, H. Deng and W.-H. Zhang, *Org. Lett.*, 2020, **22**, 7290.

7 (*a*) C. D. Vanderwal, *J. Org. Chem.*, 2011, **76**, 9555; (*b*) R. S. Paton, S. E. Steinhardt, C. D. Vanderwal and K. N. Houk, *J. Am. Chem. Soc.*, 2011, **133**, 3895; (*c*) T. M. Nguyen, M. Salvatori, R. S. del, J.-C. Wypych and C. Marazano, *J. Org. Chem.*, 2007, **72**, 5916; (*d*) Y. Genisson, C. Marazano, M. Mehmandoust, D. Gnecco and B. C. Das, *Synlett*, 1992, **5**, 431.

8 (*a*) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257; (*b*) H. Yang, E. Wang, P. Yang, H. Lv and X. Zhang, *Org. Lett.*, 2017, **19**, 5062; (*c*) K.-S. Zhou, P. Yi, T. Yang, F.-M. Yanf, K.-H. Lee, B.-Y. Zhao, Y.-H. Wang and C.-J. Tan, *Org. Lett.*, 2019, **21**, 5051; (*d*) J. Li, Y. Liu, X. Song, T. Wu, J. Meng, Y. Zheng, Q. Qin, D. Zhao and M. Cheng, *Org. Lett.*, 2019, **21**, 7149; (*e*) S. Varga, P. Angyal, G. Martin, O. Egyed, T. Holczbauer and T. Soos, *Angew. Chem., Int. Ed.*, 2020, **59**, 13547; (*f*) K. M. Lambert, J. B. Cox, L. Liu, A. C. Jackson, S. Yruegas, K. B. Wiberg and J. L. Wood, *Angew. Chem., Int. Ed.*, 2020, **59**, 9757.

9 For stereospecific cross-coupling of C–X with optically pure organometallic reagents: (*a*) L. Li, C.-Y. Wang, R. Huang and M. R. Biscoe, *Nat. Chem.*, 2013, **5**, 607; (*b*) T. Ohmura, T. Awano and M. Suginome, *J. Am. Chem. Soc.*, 2010, **132**, 13191; (*c*) G. A. Molander and S. R. Wisniewski, *J. Am. Chem. Soc.*, 2012, **134**, 16856; (*d*) Q. Zhou, H. D. Srinivas, S. Dasgupta and M. P. Watson, *J. Am. Chem. Soc.*, 2013, **135**, 3307; (*e*) G. A. Molander, S. R. Wisniewski and M. Hosseini-Sarvari, *Adv. Synth. Catal.*, 2013, **355**, 3037; (*f*) L. Li, S. Zhao, A. Joshi-Pangu, M. Diane and M. R. Biscoe, *J. Am. Chem. Soc.*, 2014, **136**, 14027; (*g*) Q. Zhou, K. M. Cobb, T. Tan and M. P. Watson, *J. Am. Chem. Soc.*, 2016, **138**, 12057; (*h*) K. R. Campos, A. Klapars, J. H. Waldman, P. G. Dormer and C. Chen, *J. Am. Chem. Soc.*, 2006, **128**, 3538; (*i*) H. M. Wisniewska, E. C. Swift and E. R. Jarvo, *J. Am. Chem. Soc.*, 2013, **135**, 9083; (*j*) J. Llveria, D. Leonori and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2015, **137**, 10958.

10 For asymmetric C–X alkylation: (*a*) S. Ge and J. F. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 16330; (*b*) N. T. Kadunce and S. E. Reisman, *J. Am. Chem. Soc.*, 2015, **137**, 10480; (*c*) D. Wang, L. Wu, F. Wang, X. Wan, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 6811; (*d*) G. J. Lovinger, M. D. Aparece and J. P. Morken, *J. Am. Chem. Soc.*, 2017, **139**, 3153.

11 For asymmetric C–H alkylation: (*a*) G. Song, W. N. O. Wylie and Z. Hou, *J. Am. Chem. Soc.*, 2014, **136**, 12209; (*b*) G. A. Molander and S. R. Wisniewski, *J. Am. Chem. Soc.*, 2012, **134**, 16856; (*c*) S. Yu, H. L. Sang and S. Ge, *Angew. Chem., Int. Ed.*, 2017, **56**, 15896; (*d*) G. Bertuzzi, D. Pecorari, L. Bernardi and M. Fochi, *Chem. Commun.*, 2018, **54**, 3977; (*e*) A. Motaleb, S. Rani, T. Das, R. G. Gonnade and P. Maity, *Angew. Chem., Int. Ed.*, 2019, **58**, 14104.

12 For racemic and asymmetric C−H aminoalkylation: (*a*) A. Kundu, M. Inoue, H. Nagae, H. Tsurugi and K. Mashima, *J. Am. Chem. Soc.*, 2018, **140**, 7332; (*b*) R. S. J. Proctor, H. J. Davis and R. J. Phipps, *Science*, 2018, **360**, 419; (*c*) X. Liu, Y. Liu, G. Chai, B. Qiao, X. Zhao and Z. Jiang, *Org. Lett.*, 2018, **20**, 6298.

13 (*a*) Md N. Alam, S. R. Dash, A. Mukherjee, S. Pandole, U. K. Marelli, K. Vanka and P. Maity, *Org. Lett.*, 2021, **23**, 890; (*b*) A. Motaleb, A. Bera and P. Maity, *Org. Biomol. Chem.*, 2018, **16**, 5081; (*c*) Md N. Alam, K. M. Lakshmi and P. Maity, *Org. Biomol. Chem.*, 2018, **16**, 8922.

14 Although these reports by Wolfe group are reported as [1,2] *aza*-Wittig, excess Lewis acid along with base is required and the authors recognize a possible Stevens pathway *via* zwitterionic ammonium intermediate: (*a*) R. K. Everett and J. P. Wolfe, *J. Org. Chem.*, 2015, **80**, 9041; (*b*) R. K. Everett and J. P. Wolfe, *Tetrahedron Lett.*, 2015, **56**, 3393.

15 The corresponding oxa-[1,2] Wittig is a well-known rearrangement, proceeds *via* a widely accepted dissociative radical pair mechanism, and exhibit substrate and reaction condition dependent variable degrees of chirality transfer: (*a*) K. Tomooka, H. Yamamoto and T. Nakai, *Liebigs Ann./Recl.*, 1997, 1275; (*b*) S. L. Schreiber and M. T. Goulet, *Tetrahedron Lett.*, 1987, **28**, 1043; (*c*) K. Tomoka, M. Kikuchi, K. Igawa, P.-H. Keong and T. Nakai, *Tetrahedron Lett.*, 1999, **40**, 1917; (*d*) K. Tomoka, H. Yamamoto and T. Nakai, *Angew. Chem., Int. Ed.*, 2000, **39**, 4500; (*e*) K. Tomoka, M. Kikuchi, K. Igawa, M. Suzuki, P.-H. Keong and T. Nakai, *Angew. Chem., Int. Ed.*, 2000, **39**, 4502; (*f*) K. Tomooka, H. Yamamoto and T. Nakai, *J. Am. Chem. Soc.*, 1996, **118**, 3317; (*g*) R. E. Maleczka Jr and F. Geng, *J. Am. Chem. Soc.*, 1998, **120**, 8551.

16 For captodative stabilization of radical intermediates, see: (*a*) H. Viehe, Z. D. Anousek and R. Merenyi, *Acc. Chem. Res.*, 1985, **18**, 148; (*b*) J. P. Peterson and A. H. Winter, *J. Am. Chem. Soc.*, 2019, **141**, 12901.

17 Stoichiometric amount of catalysts were taken for strong MHMDS base at 0 °C to avoid starting material decomposition.

18 (*a*) J. Barluenga, F. J. Fañanás, R. Sanz, C. Marcos and M. Trabada, *Org. Lett.*, 2002, **9**, 1587; (*b*) F. Gao, B.-S. Kim and P. J. Walsh, *Chem. Sci.*, 2016, **7**, 976.

19 The enantiomeric excess of salts **1** was determined by chiral HPLC after converting those to the corresponding pyridones.

20 Few chiral amines are commercially available and others were synthesized following a recent literature method: (*a*)

© 2021 The Author(s). Published by the Royal Society of Chemistry

Open Access Article. Published on 28 May 2021. Downloaded on 2/10/2026 7:54:39 PM.
This article is licensed under a Creative Commons Attribution-NonCommercial 3.0 Unported Licence.

M. Xiao, X. Yue, R. Xu, W. Tang, D. Xue, C. Li, M. Lei, J. Xiao and C. Wang, *Angew. Chem., Int. Ed.*, 2019, **58**, 10528; (*b*) V. Bagutski, T. G. Elford and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2011, **50**, 1080.

21 Cyclopropanes are known to remain intact in a radical reaction; either *via* reversible ring opening, or faster radical recombination before ring opening: (*a*) S. Umemiya, K. Nishino, I. Sato and Y. Hayashi, *Chem.–Eur. J.*, 2014, **20**, 15753; (*b*) X. Gou and O. S. Wenger, *Angew. Chem., Int. Ed.*, 2018, **57**, 2469; (*c*) J. Li, M. Kong, B. Qiao, R. Lee, X. Zhao and Z. Jiang, *Nat. Commun.*, 2018, **9**, 2445.

22 (*a*) L. Haiyan, L. Gaoping and J. Liu, WO2010075469A1, 2010; (*b*) S. Zhou and R. Tong, *Chem.–Eur. J.*, 2016, **22**, 7084; (*c*) L. Mengozzi, A. Gualandi and P. G. Cozzi, *Chem. Sci.*, 2014, **5**, 3915; (*d*) S. Zhou and R. Tong, *Org. Lett.*, 2017, **19**, 1594; (*e*) J. Yu, Z. Zhang, S. Zhou, W. Zhang and R. Tong, *Org. Chem. Front.*, 2018, **5**, 242.

23 We synthesized pyridinium salts following a modified literature protocol: G. H. R. Viana, I. C. Santos, R. B. Alves, L. Gil, C. M. Marazano and R. P. F. Gil, *Tetrahedron Lett.*, 2005, **46**, 7773.

24 For competitive [1,2] & [1,4] *oxa*-[1,4] Wittig rearrangements: F. Wang, J. Wang, Y. Zhang and J. Yang, *Tetrahedron*, 2020, **76**, 130857. For stereoretentive *oxa*-[1,2] & [1,4]: L. M. Mori-Quiroz and R. E. Maleczka Jr, *J. Org. Chem.*, 2015, **80**, 1163.

25 (*a*) J. P. Perdew, K. Burke and M. Ernzerhof, *Phys. Rev. Lett.*, 1996, **77**, 3865; (*b*) K. Eichkorn, F. Weigend, O. Treutler and R. Ahlrichs, *Theor. Chem. Acc.*, 1997, **97**, 119; (*c*) R. Ahlrichs, M. Bar, M. Haser, H. Horn and C. Kolmel, *Chem. Phys. Lett.*, 1989, **162**, 165.

26 (*a*) H.-Y. Yoo, K. N. Houk, J. K. Lee, M. A. Scialdone and A. I. Meyers, *J. Am. Chem. Soc.*, 1998, **120**, 205; (*b*) F. Haeffner, K. N. Houk, S. M. Schulze and J. K. Lee, *J. Org. Chem.*, 2003, **68**, 92310.

27 (*a*) W. Li, W. Xu, J. Xie, S. Yu and C. Zhu, *Chem. Soc. Rev.*, 2018, **47**, 654; (*b*) X. Wu and C. Zhu, *Acc. Chem. Res.*, 2020, **53**, 1620; (*c*) Z. Feng and D. J. Tantillo, *J. Am. Chem. Soc.*, 2021, **143**, 088.

28 (*a*) F. D. Greene, M. A. Berwick and J. C. Stowell, *J. Am. Chem. Soc.*, 1970, **92**, 867; (*b*) S. L. Shevick, C. V. Wilson, S. Kotesova, D. Kim, P. L. Holland and R. Shenvi, *Chem. Sci.*, 2020, **11**, 12401.

© 2021 The Author(s). Published by the Royal Society of Chemistry