frontiers in Chemistry

ORIGINAL RESEARCH
published: 08 September 2021
doi: 10.3389/fchem.2021.742399

Regio- and Diastereoselective Vicinal Aminobromination of Electron Deficient Olefins via Phosphorus-Based GAP Protocol

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Chemical synthesis based on Group-Assisted Purification chemistry (GAP) has been prolifically used as a powerful, greener and ecofriendly tool so far. Herein, we report hypervalent iodine (III) mediated regio- and diastereoselective aminobromination of electron-deficient olefins using group-assisted purification (GAP) method. By simply mixing the GAP auxiliary-anchored substrates with $TsNH_2$–NBS as nitrogen/bromine sources and $PhI(OAc)_2$ as a catalyst, a series of vicinal bromoamines with multifunctionalities were obtained in moderate to excellent yields (53–94%). The vicinal bromoamines were obtained without column chromatography and/or recrystallization simply by washing the crude mixtures with cosolvents and thus avoiding wastage of silica, solvents, time, and labor. The GAP auxiliary is recyclable and reusable.

Keywords: aziridinium, diastereoselectivity, iodobenzene diacetate, nitrogen/halogen source, protecting groups

OPEN ACCESS

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Specialty section:
This article was submitted to Organic Chemistry, a section of the journal Frontiers in Chemistry

Received: *16 July 2021*
Accepted: *09 August 2021*
Published: *08 September 2021*

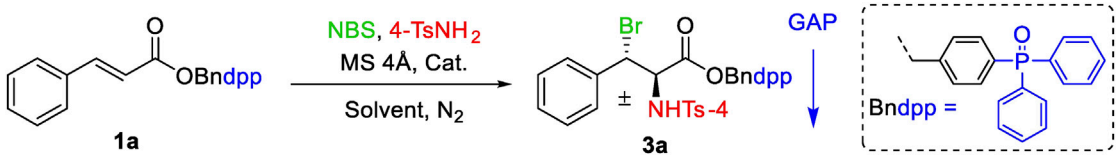
Citation:
Rahman AU, Zarshad N, Khan I, Faiz F, Li G and Ali A (2021) Regio- and Diastereoselective Vicinal Aminobromination of Electron Deficient Olefins via Phosphorus-Based GAP Protocol. Front. Chem. 9:742399. doi: 10.3389/fchem.2021.742399

INTRODUCTION

Aminohalogenation of olefins, an important difunctionalization reaction, allows the direct construction to C–N and C–halogen double bonds which are versatile synthetic intermediates for pharmaceutically and biologically important molecules (Gao et al., 2005; Yeung et al., 2006b). The intramolecular and/or intermolecular replacement of labile halogen moieties with multifarious nucleophiles leads to precursors like vicinal diamines, lactams, amino alcohols α,β-dehydroamino acids, amino aldehydes and aziridines (Ling et al., 1996; Van and De Kimpe, 2000; Klepacz and Zwierzak, 2001; Chen et al., 2005; Li et al., 2007; Ghorai et al., 2011; Schröder et al., 2017; Thakur et al., 2017).

Since the aminohalogenation reaction was discovered several decades ago, a variety of synthetic techniques have been created to provide this capability. Various reagent systems (halogen/nitrogen sources) such as $TsNH_2$–NBS (Thakur et al., 2003; Chen et al., 2009a; Chen et al., 2009b; Shaikh et al., 2009; Wei et al., 2009a; Wei et al., 2009b; Cai et al., 2011; Yu et al., 2017), cyanamide–NBS (Ponsold and Ihn, 1970), N-bromoacetamide (Yeung et al., 2006a; Yeung et al., 2006b), N,N-dihalosulfonamides (Kharasch and Priestley, 1939), S,S-dimethyl-N-(p-toluenesulfonyl) sulfilimine–NBS (Raghavan et al., 2001), $BocNH_2$/$BocNBr_2$ (Chen et al., 2013), N,N-dihalocarbamates (Śliwińska and Zwierzak, 2003) and N-halocarbamates (Driguez et al., 1978) have been designed to carry out this transformation. To achieve high yields, excellent

TABLE 1 | Optimization of the reaction conditions.[a]



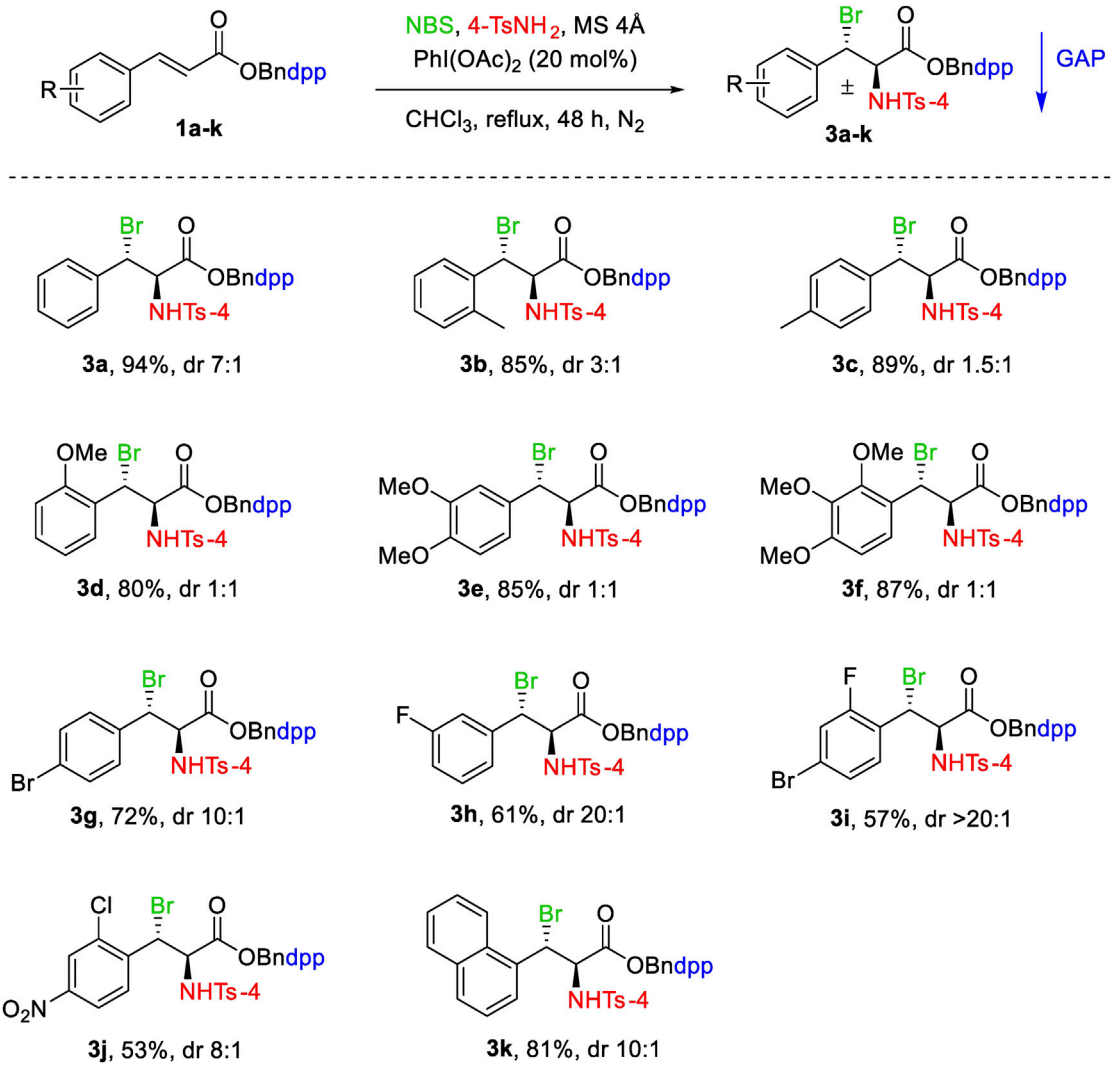
Entry	Catalyst	Br source (equiv.)	Time (h)	Solvent	Yield[b] (%)	dr[c]
1		NBS (1.5)	24	CH_2Cl_2	60	7:1
2		TBCO (1.5)	24	CH_2Cl_2	31	5:1
3		PhCONHBr (1.5)	24	CH_2Cl_2	47	4:1
4		DBDMH (1.5)	24	CH_2Cl_2	53	4:1
5	$Pd(OAc)_2$	NBS (1.5)	24	CH_2Cl_2	69	10:1
6	$Mn(OAc)_2$	NBS (1.5)	24	CH_2Cl_2	60	4:1
7	$FeCl_3$	NBS (1.5)	24	CH_2Cl_2	54	4:1
8	$PhI(OAc)_2$	NBS (1.5)	24	CH_2Cl_2	78	7:1
9	$ZnCl_2$	NBS (1.5)	24	CH_2Cl_2	35	6:1
10	CuI	NBS (1.5)	24	CH_2Cl_2	52	10:1
11	$Cu(Otf)_2$	NBS (1.5)	24	CH_2Cl_2	63	7:1
12	$Sc(Otf)_3$	NBS (1.5)	24	CH_2Cl_2	51	4:1
13[e]	$PhI(OAc)_2$	NBS (1.5)	24	CH_2Cl_2	82	7:1
14[e]	$PhI(OAc)_2$	NBS (2.0)	24	CH_2Cl_2	85	7:1
15[e]	$PhI(OAc)_2$	NBS (2.0)	48	CH_2Cl_2	90	7:1
16[e]	PhI(OH) (4-TsOH)	NBS (2.0)	48	CH_2Cl_2	70	8:1
17[e]	$PhI(OCOCF_3)_2$	NBS (2.0)	48	CH_2Cl_2	74	8:1
18[e]	$PhI(OAc)_2$	NBS (2.0)	48	CH_3CN	77	7:1
19[e]	$PhI(OAc)_2$	NBS (2.0)	48	$CHCl_3$	94	7:1
20[e]	$PhI(OAc)_2$	NBS (2.0)	48	PhMe	28	
21[e]	$PhI(OAc)_2$	NBS (2.0)	48	THF	–	–
22[e]	$PhI(OAc)_2$	NBS (2.0)	48	Et_2O	–	–
23[e]	$PhI(OAc)_2$	NBS (2.0)	48	EtOAc	–	–
24[e,f]	$PhI(OAc)_2$	NBS (2.0)	48	$CHCl_3$	61	7:1

[a]*Unless otherwise specified, all reactions were performed with 0.15 mmol of 11a, 20 mol% of the catalyst, 4-TsNH$_2$ and Br source (1:1), 75 mg of MS 4 Å in 1.5 ml of solvent at room temperature under N$_2$.*
[b]*Isolated yields with GAP washing (for entries 2, 3, 9 and 20 GAP washing was not conducted).*
[c]*The dr values were determined by the analysis of.*
[d]*H NMR spectra.*
[e]*For entries 13–23, the reactions were performed at reflux.*
[f]*The reaction was carried out at 10 mol% of the catalyst.*

regioselectivities and diastereoselectivities, our group as well as others have developed efficient catalytic systems which comprise: metal and nonmetal powders (Chen et al., 2009b; Wei et al., 2009a), metal oxides (Thakur et al., 2003; Shaikh et al., 2009) and metal salts (Albone et al., 1998; Ando et al., 1998; Li et al., 1999; Li et al., 2000; Wei et al., 2001; Yeung et al., 2006a; Wang et al., 2008; Chen et al., 2009a; Wei et al., 2009b; Yadav et al., 2009), organic catalysts like hypervalent iodines (Fan et al., 2007; Wang and Wu, 2007; Wu et al., 2008), phosphoric acid or phosphate (Chen et al., 2010; Huang et al., 2011; Alix et al., 2012; Xie et al., 2013), noncatalytic routes which utilize Bronsted acids (Wu and Wang, 2007) such as H_2SO_4 or ionic liquid media [Bmim][BF_4](Xu et al., 2004). Though considerable progress has been made in this area, drastic reaction conditions, procedural complexities, the use of metal catalysts and contamination of materials by metal traces (Chen et al., 2003a; Garrett and Prasad, 2004; Huang and Shaughnessy, 2006) limit their application. Besides, the study of efficient highly regio- and stereoselective methods which could reduce the formation of side products remains challenging. Purification techniques such as column chromatography and recrystallization are commonly used in the above mentioned syntheses.

The development of environmentally benign and eco-friendly greener reaction protocol is ubiquitous both in academia and the pharmaceutical industry (Shi et al., 2008). GAP chemistry, recently introduced by our group, fulfills the afford-mentioned criteria of greener chemistry by avoidance of separation, workup, recrystallization, and column chromatography. The product is obtained by merely washing the reaction mixture with a combination of more polar and less polar solvents (Wang et al., 2013; Chennapuram et al., 2014; Dommaraju and Prajapati, 2015; Seifert et al., 2016; Patel et al., 2019; Li et al., 2020a; Li et al., 2020b; Li et al., 2020c). Polarity difference between the solvents plays a key role in the isolation of products, i.e., the impurities get dissolved in washing solvents and the GAP-coupled product remains insoluble clustered together. Keeping in view the greener aspect of GAP chemistry, here we report for the first time hypervalent iodine (III) mediated regio- and

TABLE 2 | Substrate scope of aminobromination of N-(4-(diphenylphosphoryl)benzyl) cinnamates 1a-k.



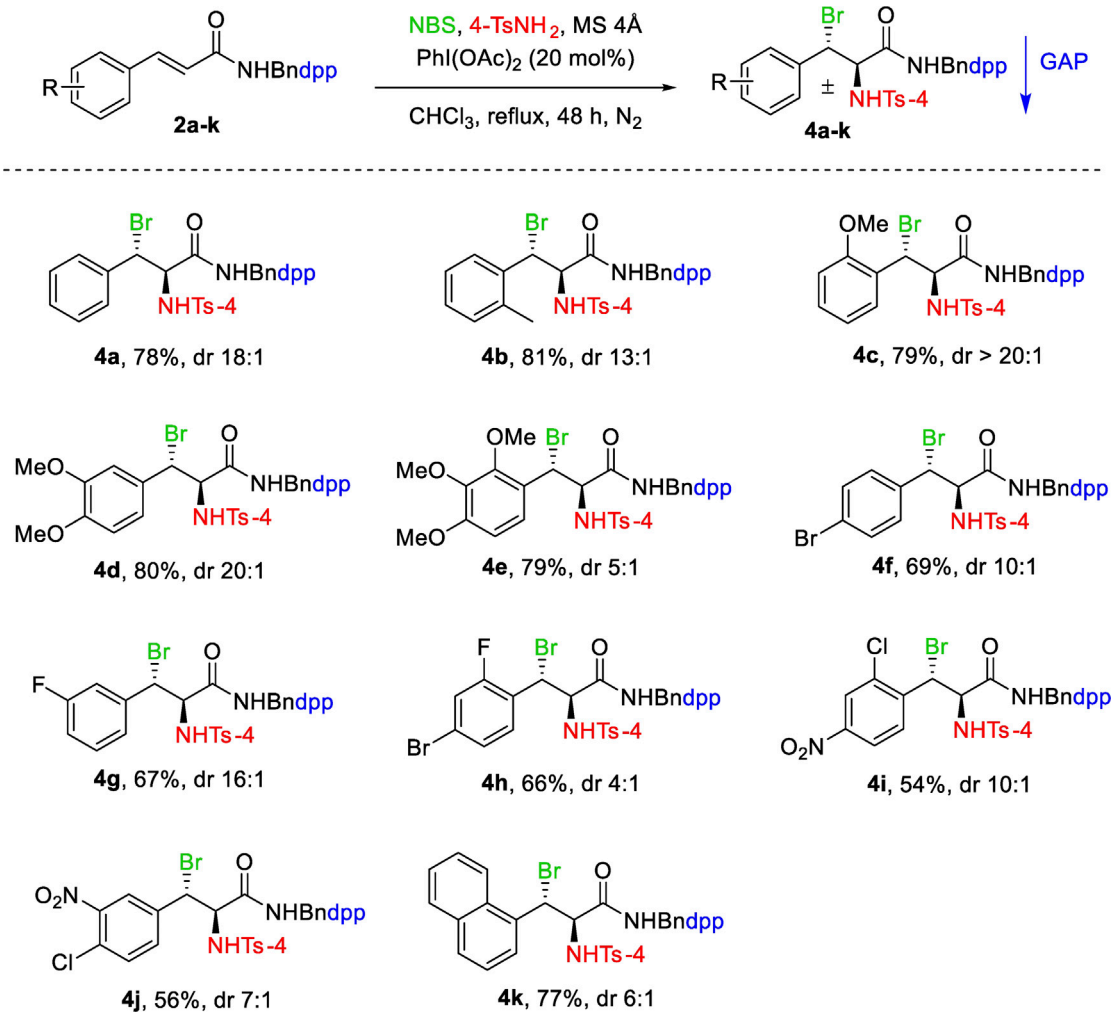
Unless otherwise specified, all reactions were performed with 0.3 mmol of 1a-k, 0.6 mmol of 4-TsNH$_2$, 0.6 mmol of NBS, 150 mg of MS 4Å in 3 ml of chloroform at reflux under N$_2$. The dr values were determined by the analysis of ^{1}H NMR spectra. Isolated yields with GAP washing.

diastereoselective vicinal aminobromination of GAP-tailored electron-deficient olefins via GAP protocol.

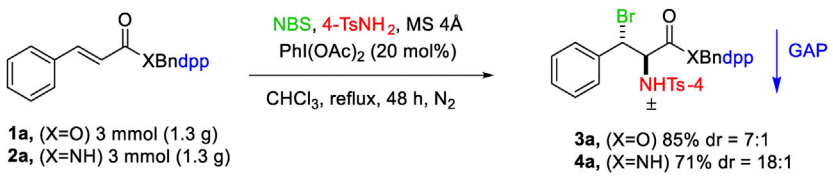
RESULTS AND DISCUSSION

Based on our prior research, we were interested in aminobromination of α,β-unsaturated cinnamic acids, which are challenging due to the formation of regio- and diastereomeric products. To develop conditions for regio- and diastereoselective transformation, we began to prepare the GAP coupled intermediate 1a-k and 2a-k in our laboratory according to the literature procedure (Rahman et al., 2020) given in supporting information. To optimize the reaction conditions, we initiated the study with the GAP anchored intermediate 1a as the test substrate, p-toluenesulfonamide (4-TsNH$_2$) and N-bromosuccinimide (NBS) as the nitrogen and bromine source respectively. To our delight, product 3a was isolated in 60% yield after 24 h with a dr value 7:1 when 1a was treated with NBS (1.5 eq) and 4-TsNH$_2$ (1.5 eq) in dichloromethane at room temperature without any catalyst. Lower yields were obtained with other bromine sources (**Table 1**, entries 2–4). With NBS as the bromine source, a series of hypervalent iodine and transition metal catalysts were subsequently employed. The yield was significantly improved with iodobenzene diacetate (PhI(OAc)$_2$), and aminobromine product was isolated in a chemical yield of 78% with diastereoselective ratio of 7:1 (**Table 1**, entry 8). Refluxing this reaction mixture further

TABLE 3 | Substrate scope of aminobromination of N-(4-(diphenylphosphoryl)benzyl) cinnamamides 2a-k.

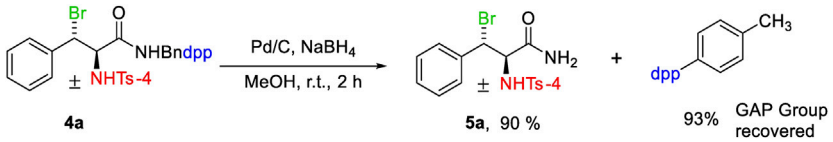


Unless otherwise specified, all reactions were performed with 0.3 mmol of 2a-k, 0.6 mmol of 4-TsNH$_2$, 0.6 mmol of NBS, 150 mg of MS 4Å in 3 ml of chloroform at reflux under N$_2$. The dr values were determined by the analysis of ^{1}H NMR spectra. Isolated yields with GAP washing.

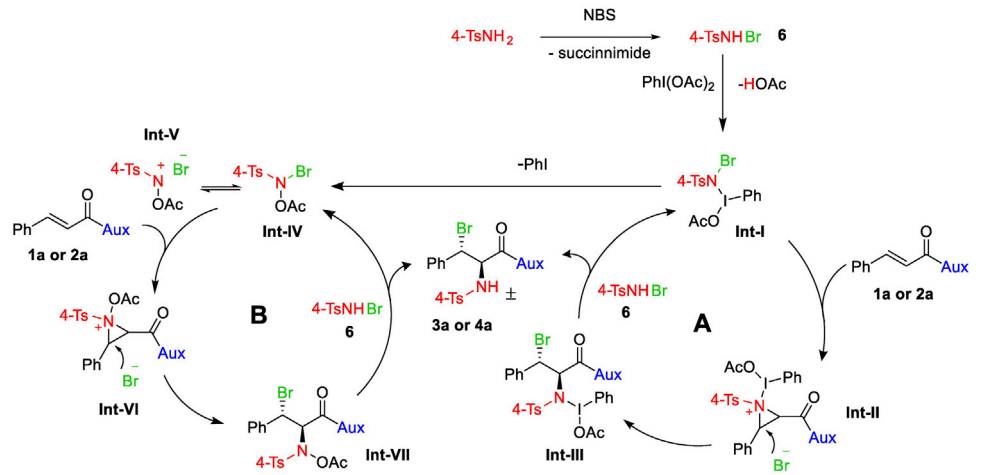


SCHEME 1 | Gram scale reactions.

enhanced the yield up to 82% (**Table 1**, entry 13). An even more increase in yield was observed when 2 eq of each NBS and 4-TsNH$_2$ was added to the reaction medium (**Table 1**, entry 14). The yield was further improved to 90% with a longer reaction time (48 h) (**Table 1**, entry 15). We then utilized the catalytic activity of other iodine catalysts like PIFA (PhI(OCOCF$_3$)$_2$) and Koser's reagent (PhI(OH) (4-TsOH)) in this transformation; only PhI(OAc)$_2$ could give the terminal product in higher yield (**Table 1**, entry 15). Except for CHCl$_3$ and CH$_3$CN, poorer results were obtained at reflux temperature with other solvents examined when the reaction was performed with 20 mol% of PhI(OAc)$_2$ as the catalyst and 2 equiv. of NBS and 4-TsNH$_2$



SCHEME 2 | GAP deprotection.



SCHEME 3 | A possible pathway for the synthesis of vicinal bromoamines.

(**Table 1**, entries 18–23). A yield of 67% was obtained when the catalyst loading was decreased to 10 mol%. Control experiments showed that both NBS and the 4-$TsNH_2$ were important for the reaction and that using activated molecular sieves 4Å generally increased the yield and selectivity.

After optimizing the conditions for aminobromination reaction, the substrate scope was subsequently explored. The results are shown in **Table 2**. A wide range of N-(4-(diphenylphosphoryl) benzyl) cinnamates 1a-k bearing different aryl groups with a variety of electron-donating (EDG) (such as methyl and methoxy) and electron-withdrawing groups (EWG) (floro, chloro bromo, nitro) were investigated which provided moderate to high yields (53–94%). As shown in **Table 2**, with regards to the EDG on the aromatic ring of cinnamic substrates 1b-1f, the addition reactions were well tolerated to produce the relevant adducts in good yields (**Table 2**, 2b-2f). Both the substrates 1b and 1c with an ortho-MeC_6H_4 and a para-MeC_6H_4 group delivered the corresponding products 3b and 3c smoothly in 85 and 89% yields respectively. Similarly, the product 3 days with ortho-$OMeC_6H_4$ was isolated in a high yield of 80%. The di-OMe and tri-OMe substituted substrates were even more effective for the reaction (**Table 2**, 3e, 3f). On the other hand, substrates bearing EWG on the aromatic rings generally decreased the yield under the same conditions (**Table 2**, 3g-3j). Importantly, halogen (Br or F) groups were almost consistent with the conditions, offering 3g, 3h and 3i in moderate yields. The lowest yield of 53% was obtained for 3j, which had a Cl group at the ortho-position and an NO_2 group at para-position. The substrate with a naphthyl group reduced the yield to 81% under the same conditions but enhanced the diastereoselectivity (**Table 2**, 3k).

In addition to N-(4-(diphenylphosphoryl) benzyl) cinnamates, N-(4-(diphenylphosphoryl) benzyl) cinnamamides 2a-k were then exposed to aminobromination under the optimized reaction conditions for 1a-k. The reaction was applicable in the presence of 20 mol% of $PhI(OAc)_2$ in chloroform, substrate 2a was successfully converted in 48 h at reflux temperature to haloamine product 4a in 78% yield with a diastereoselective ratio of 18:1.

As shown in **Table 3**, this transformation can be extended to a variety of N-(4-(diphenylphosphoryl)benzyl) cinnamamides 2a-k to provide moderate to high yields (56–81%). The substrates with EWG and EDG display substantial variations in reaction reactivity and regioselectivity. Aminobromination was greatly facilitated by the presence of a strong EDG on the benzene ring, affording products in high yields and good to excellent diastereoselectivity (**Table 3**, 4b–4e). The substrate with EWG on the aromatic ring, as expected, resulted in a lower yield (**Table 3**, 4f–4j). The substrate with a naphthyl group, however, had no significant effect on the yield under the same conditions and lowered the diastereoselectivity (**Table 3**, 4k).

From **Table 2**, **3**, we further observed that EWG and EDG on the benzene ring had a significant impact on the diastereoselectivity of cinnamates and cinnamamides which is generally governed by the GAP auxiliaries. In the case of cinnamates, EDG resulted in low diastereoselectivity than EWG. For cinnamamides, however, EDG had higher diastereoselectivity than EWG. This variation in

diastereoselectivity of both derivatives could be attributed to stereoelectronic factors.

The feasibility of this procedure was studied by conducting the reaction on a gram scale for the starting materials 1a and 2a, which resulted in 85 and 73% yields for the products 3a and 4a, respectively.

In the presence of Pd/C and $NaBH_4$, the GAP-tailored vicinal aminobromine was deprotected which afforded Bndpp in 93% yield (**Schemes 1**,**2**). The mixture is dissolved in a small volume of a solvent, such as ethyl acetate or DCM, and then petroleum ether is used to purify the products. The GAP auxiliary precipitates as a white solid that is filtered and treated with petroleum ether. To achieve the desired β-bromoamine as a white substance, the filtrate is evaporated under a vacuum.

Mechanism

The outcomes of various experimentation within our research team, as well as other (Li et al., 2001; Wei et al., 2001; Wang and Wu, 2007; Wu and Wang, 2008; Chen et al., 2009a), lead to the conclusion that NBS may react with 4-$TsNH_2$ to generate N-bromo-p-toluenesulfonamide (4-TsNHBr) 6 (**Scheme 3**), which would be oxidized by $PhI(OAc)_2$ to generate intermediate Int-I that may either follow cycle A or cycle B. In cycle A, the Int-I will form aziridinium Int-II with a double bond of 1a or 2a, which is then stereoselectively attacked by the dissociated bromide from the Int-I at the more electrophilic carbon (beta to carbonyl carbon) to yield compound Int-III. Int-III and 16 eventually provide the ultimate bromoamine substance 3a or 4a and restore Int-I. When the fragile N–I bond of Int-I is broken, N-acetoxy-N-halo-p-toluenesulfonamide Int-IV can form, which could then be the active intermediate for cycle B. Int-IV that forms an equilibrium with nitrenium ion Int-V (Kikugawa et al., 2003; Murata et al., 2008) could react with olefin 1a or 2a to afford aziridinium Int-VI which would lead to Int-VII following an S_N2 nucleophilic attack by the nearby bromide. Finally, the reaction of the intermediate Int-VII with 6 gives the final product and regenerates Int-IV.

Benefiting from the present methodology and this mechanism analysis, the utilizations of GAP chemistry for aminohalogenation and diamination of a broader scope of substrates (Chen et al., 2003b; Chen et al., 2004), in search for new chirality (Wu et al., 2019a; Wu et al., 2019b; Liu et al., 2020) and on multi-component reactions will be further conducted in our labs (Jiang et al., 2012a; Jiang et al., 2012b).

EXPERIMENTAL SECTION

Aminobromination of 4-(Diphenylphosphoryl) Benzyl Cinnamates 1a-k and N-(4-(Diphenylphosphoryl) Benzyl) Cinnamamides 2a-k

Typical procedure: Into a dry vial was added 1a or 2a (1 mmol, 1 eq), NBS (356 mg, 2 mmol, 2 eq), 4-$TsNH_2$ (342 mg, 2 mmol, 2 eq), $PhI(OAc)_2$ (64 mg, 20 mol%) and freshly activated 4 Å molecular sieves (500 mg) and capped under nitrogen protection. $CHCl_3$ (3 ml) was added via a syringe and the reaction mixture was allowed to reflux for 48 h. After completion (monitored by TLC), the reaction was quenched with dropwise addition of saturated aqueous Na_2SO_3 solution (2 ml) and DCM (3 × 10 ml) was added to extract the product. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The mixture was redissolved in the minimal amount of solvents like ethyl acetate or DCM, and then petroleum ether was added. The GAP auxiliary precipitated in the form of a white solid which was filtered and washed with petroleum ether. The filtrate is evaporated under a vacuum to obtain the desired β-aminobromine as a white product.

General Procedure for Deprotection of Group-Assisted Purification Auxiliary BnDpp.

To a 10 ml round bottom flask was added 4a (0.2 g, 0.32 mmol), 10 wt% Pd/C (20 mg) 2 ml MeOH and $NaBH_4$ (15.2 mg, 2 equiv.). To prevent the loss of produced hydrogen and overpressure in the flask, it was sealed with a rubber septum and a deflated balloon. the reaction mixture was drained through a Celite after 2 h and the filtrate was concentrated under reduced pressure before being redissolved in EtOAc. After that, $KHSO_4$ was used to neutralize the reaction mixture. The organic layer was separated, dried over anhydrous Na_2SO_4 and evaporated to dryness to afford crude GAP auxiliary, which was easily purified using the GAP washing method.

CONCLUSION

In conclusion, we have demonstrated a new method for the preparation of vicinal aminobrominated products of electron-deficient olefins coupled with GAP auxiliaries dppBnOH and $dppBnNH_2$. Good yields and diastereoselectivities were obtained in a clean and eco-friendly reaction condition comprising the catalyst $PhI(OAc)_2$ with NBS and 4-$TsNH_2$ as the bromine and nitrogen sources. The Group-Assisted Purification (GAP) chemistry was successfully applied and the compounds were obtained as precipitates without column chromatography and recrystallization by merely adding ethyl acetate and petroleum ether. Besides, the GAP auxiliary can be recovered for reuse.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

GL, AA and AR designed the project. AR, NZ, IK and FF performed the experiments. AA and AR analyzed the data and wrote the manuscript. GL supervised, funded and critically reviewed manuscript.

FUNDING

We would like to acknowledge the financial support from the National Natural Science Foundation of China (No. 22071102 and 91956110) and Robert A. Welch Foundation (D-1361, United States).

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fchem.2021.742399/full#supplementary-material

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