



Hypervalent Iodine (III) Catalyzed Regio- and Diastereoselective Aminochlorination of Tailored Electron Deficient Olefins via GAP Chemistry

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Herein, we report a protocol for highly efficient hypervalent iodine (III) mediated, group-assisted purification (GAP) method for the regioselectivities and stereoselective aminochlorination of electron-deficient olefins. A series of vicinal chloramines with multifunctionalities were acquired in moderate to excellent yields (45–94%), by merely mixing the GAP auxiliary-anchored substrates with dichloramine T and tosylamide as chlorine/nitrogen sources and iodobenzene diacetate as a catalyst. The vicinal chloramines were obtained without any column chromatographic purification and recrystallization simply by washing the reaction mixture with a minimum amount of common inexpensive solvents and thus avoiding wastage of silica, solvents, time, and labor. The GAP auxiliary is recyclable and reusable. This strategy is easy to handle, cost-effective, greener, sustainable, environmentally benign, and mostly suitable for the syntheses of vicinal haloamines from various electron-deficient alkenes.

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

INTRODUCTION

Aminohalogenation of olefins is one of the most effective approaches to produce functional α,β -haloamines. These vicinal haloamines are versatile components in organic synthesis as their halogen moieties are labile to cross-coupling and substitution reactions. For example, haloamines are direct precursors to vicinal diamines (Ghorai et al., 2011; Xiong et al., 2014), α,β -dehydroamino acids (Chen et al., 2005), and aziridines (Van and De Kimpe, 2000; Schröder et al., 2017; Thakur et al., 2017). While the aminohalogenation is established for almost five decades now, it still faces shortcomings and limitations related to controlling regioselectivities and stereoselectivities, forming side products, which sometimes makes purification more difficult (Thakur et al., 2003; Bovino and Chemler, 2012).

Several research groups have made great contributions in developing both intermolecular and intramolecular aminohalogenation (Minakata et al., 2006; Li et al., 2007; Michael et al., 2008; Chen et al., 2010; Denmark et al., 2012; Yin et al., 2012; Chemler and Bovino, 2013; Song et al., 2013, 2016; Martínez and Muñiz, 2014; Broggini et al., 2015; Qin et al., 2015; Zhu et al., 2015; Legnani et al., 2018; Cai et al., 2019), in which a series of halogen/nitrogen sources, such as CFBSA (Pu et al., 2016), NCS/MeCN (Tay et al., 2013), NCP (Zhu et al., 2018), NFSI/TMSCl (Arteaga et al., 2018), TsNCl₂ (Han et al., 2007; Wu and Wang, 2008; Wei et al., 2009), TsNHCl (Cai et al., 2011), TsNNaCl (Martínez and Muñiz, 2014), 2-NsNNaCl (Li et al., 2001), or the combination of 2-NsNCl₂ and 2-NsNHNa (Liu et al., 2006), and so on, were employed for many types of alkene substrates. Most of these aminohalogenation systems take advantage of metals or organic catalysts to give good yields and excellent regioselectivities and diastereoselectivities. The aforementioned synthesis usually involves the use of traditional methods of purification such as column chromatography and recrystallization. Herein, in this report, we would like to present the design of new group-assisted purification (GAP) group-attached olefin substrates and their potentials for aminochlorination enabling ste minimized, greener GAP workup, and purification.

The development of greener methodologies and technologies in chemical and pharmaceutical synthesis is of utmost importance to achieve safer, faster, and economical production outcomes (Trost, 1991; Lee and Robinson, 1995; Schreiber, 2000; Tietze et al., 2008; Anderson, 2012). Recently, our group has established a concept called GAP chemistry for greener synthesis

where functionalities of special interest are incorporated into the substrates to facilitate the purification of crude products based on solubility without column chromatography or recrystallization. The pure products can be readily obtained simply by washing the crude mixture with common solvents or cosolvents (Wang et al., 2013; Chennapuram et al., 2014; Dommaraju and Prajapati, 2015; Seifert et al., 2016; Patel et al., 2019). Indeed, GAP chemistry would be the first concept consisting of both chemical aspects (reagent and reaction) and physical aspects (separation and purification). The study on GAP chemistry needs to consider solubility, stability, reactivity, and other properties of GAP reagents and products. More interestingly, we have found that, for some synthesis, GAP functional groups not only can make workup and purification easier but also can increase chemical yields, sometimes resulting in quantitative yields, which is defined as group-assisted synthesis chemistry (Seifert, 2017).

A ubiquitous requirement of GAP methodology is the sufficient solubility of products, which depends on the functional groups of their reactants. The GAP-anchored products have to dissolve in polar solvents such as THF, DCM for further reactions but remain insoluble in less polar solvents such as hexane, ether, and so on. The GAP compounds should exhibit adequate reactivity toward many reactants as well. Chiral GAP groups also control asymmetric addition efficiently. Herein, we report the GAP auxiliaries, which are labile to structural modifications to control the solubility, stability, and chemical reactivity of the products. Besides, these GAP auxiliaries can be easily deprotected via reduction or hydrolysis. Group-assisted purification chemistry has thus shown its potential to revolutionize the

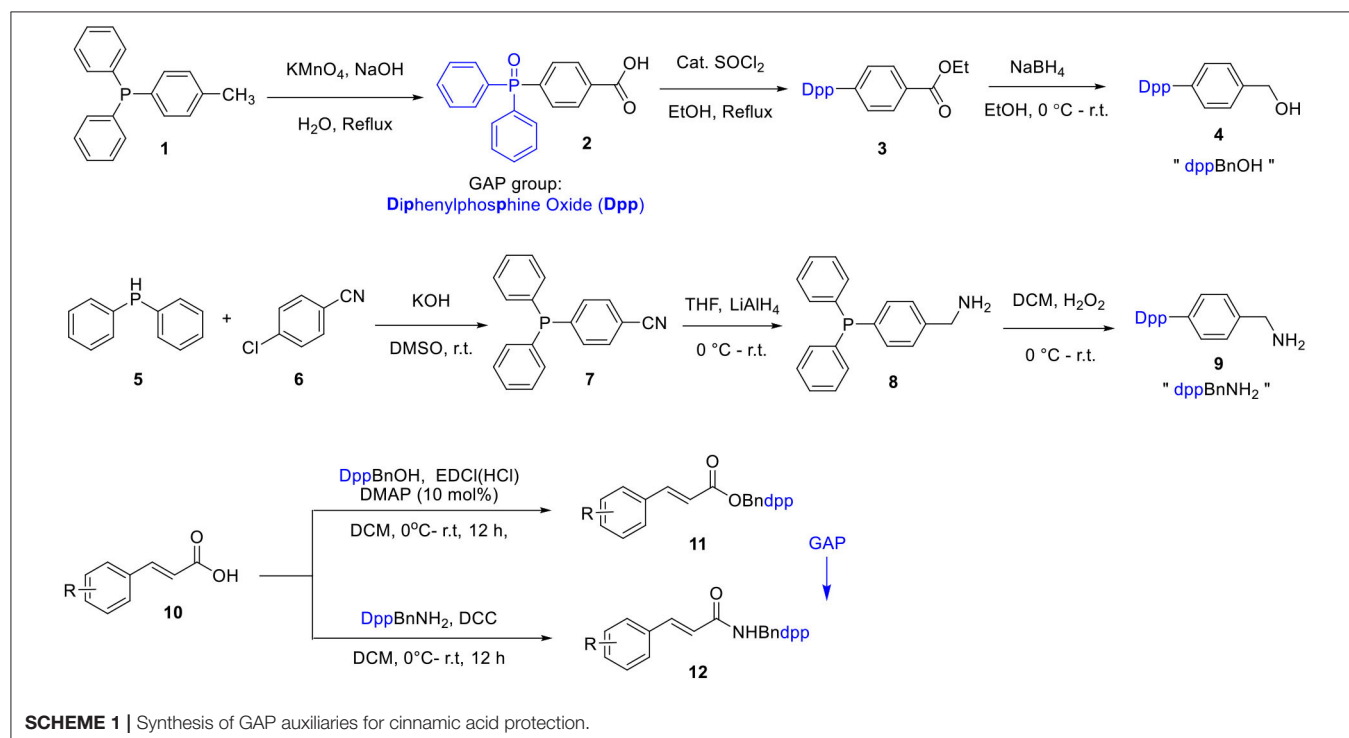


TABLE 1 | Optimization of the reaction conditions^[a].

Entry	Cat. (20 mol%)	4-TsNCl ₂	4-TsNH ₂	Yield (%) ^[b]	dr ^[c]
1	–	1.5 eq	–	–	–
2	Cu(OTf) ₂	1.5 eq	–	–	–
3	FeCl ₃	1.5 eq	–	–	–
4	PhI(OAc) ₂	1.5 eq	–	–	–
5	Pd(OAc) ₂	1.5 eq	–	–	–
6	Mn(OAc) ₂	1.5 eq	–	–	–
7	CuI	1.5 eq	–	–	–
8	ZnCl ₂	1.5 eq	–	–	–
9	PhI(OAc) ₂	1.5 eq	1.5 eq	71	8:1
10	Pd(OAc) ₂	1.5 eq	1.5 eq	30	10:1
11	Mn(OAc) ₂	1.5 eq	1.5 eq	–	–
12	FeCl ₃	1.5 eq	1.5 eq	34	4:1
13	ZnCl ₂	1.5 eq	1.5 eq	24	6:1
14	CuI	1.5 eq	1.5 eq	63	10:1
15	Cu(OTf) ₂	1.5 eq	1.5 eq	61	8:1
16	PhI(OAc) ₂	2.0 eq	2.0 eq	76	8:1
17 ^[d]	PhI(OAc) ₂	2.0 eq	2.0 eq	83	8:1
18 ^[e]	PhI(OAc) ₂	2.0 eq	2.0 eq	78	8:1

^[a]Unless otherwise specified, all reactions were performed with 0.15 mmol of **11**, 20 mol% of the catalyst, 750 mg of MS 4 Å in 1.5 mL of CH₂Cl₂ at room temperature under Ar.

^[b]Isolated yields with GAP washing (for 10, 12, and 13, GAP washing was not conducted).

^[c]The dr values were determined by the analysis of ¹H and ³¹P NMR spectra.

^[d]The reaction was performed at reflux.

^[e]The reaction was performed in the absence of 4 Å molecular sieves at reflux.

TABLE 2 | Further optimization^[a].

Entry	Solvent	Time (h)	x	Yield (%) ^[b]	dr ^[c]
1	CH ₂ Cl ₂	48	20	83	8:1
2	CHCl ₃	48	20	80	8:1
3	CH ₃ CN	48	20	50	10:1
4	PhMe	48	20	24	7:1
5	Et ₂ O	48	20	–	–
6	THF	48	20	–	–
7	DCE	48	20	48	4:1
8	DMF	48	20	–	–
9	MeOH	48	20	–	–
10	Dioxane	48	20	Traces	–
11	CH ₂ Cl ₂	24	20	77	8:1
12	CH ₂ Cl ₂	72	20	83	8:1
13	CH ₂ Cl ₂	48	10	27%	8:1

^[a]Unless otherwise specified, all reactions were performed with 0.15 mmol of **11**, 0.3 mmol of 4-TsNCl₂, 0.3 mmol of 4-TsNH₂, 750 mg of MS 4 Å in 1.5 mL of solvent at reflux under Ar.

^[b]Isolated yields with GAP washing (for 4 and 13, GAP washing was not conducted).

^[c]The dr values were determined by the analysis of ¹H and ³¹P NMR spectra.

pharmaceutical industry as it saves time, manpower, and costs in safer manners.

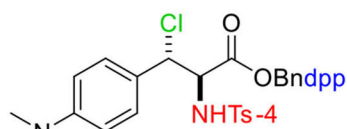
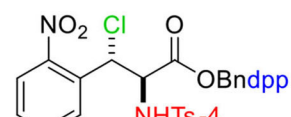
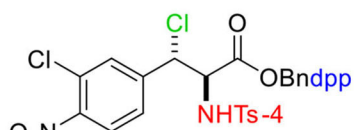
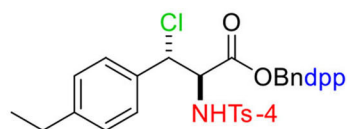
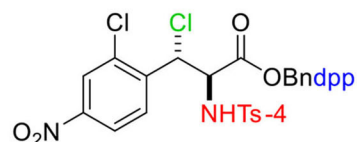
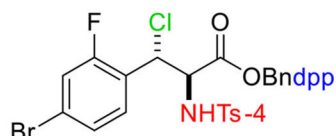
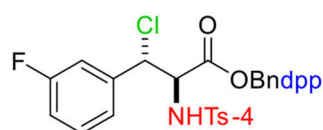
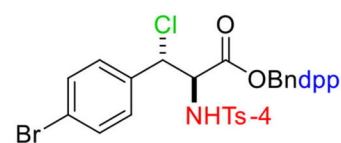
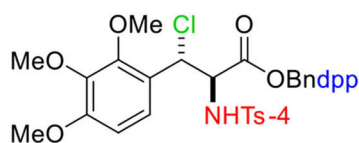
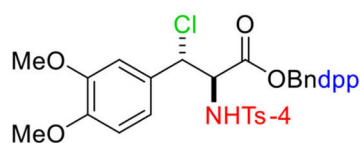
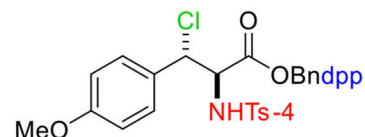
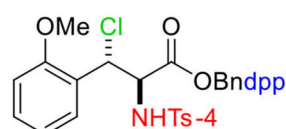
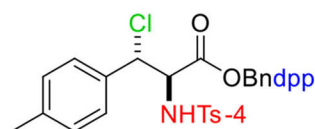
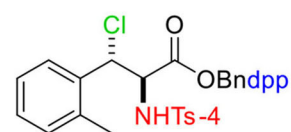
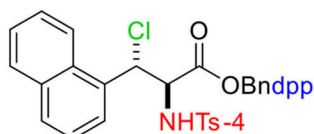
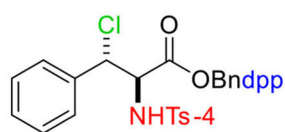
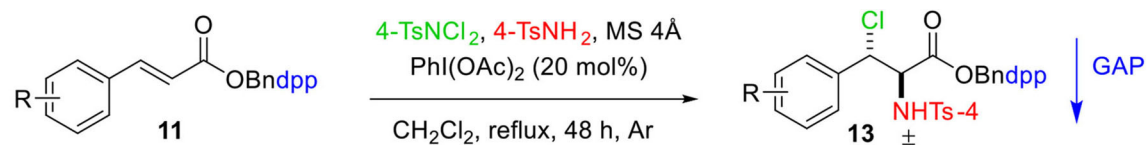
RESULTS AND DISCUSSION

We initiated the study by investigating GAP auxiliaries and their potential application in GAP chemistry. In our previous

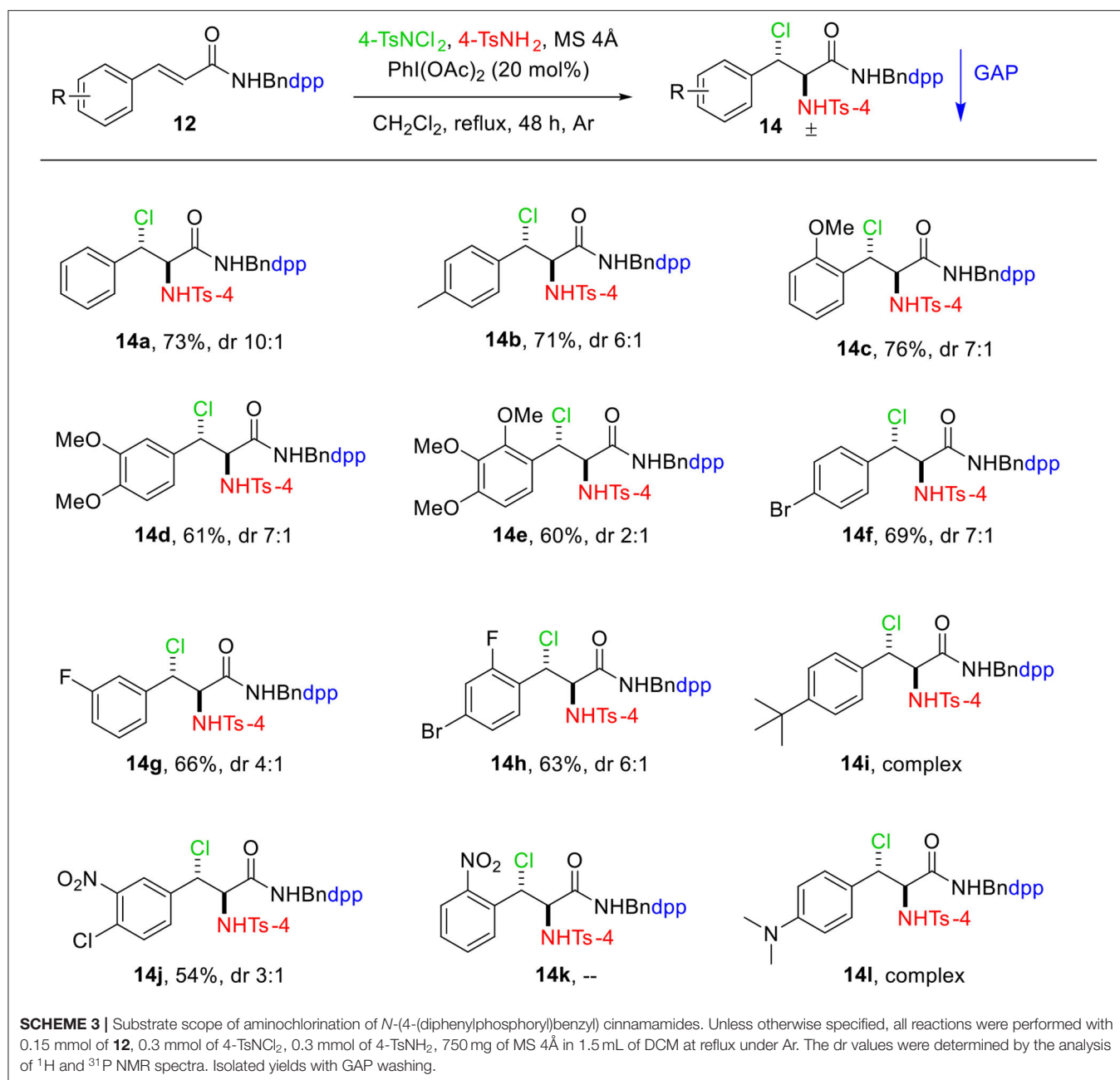
work, diphenylphosphine oxide (abbreviated as Dpp) was proven to be a stable GAP candidate. Its synthesis began with the benzylic and phosphine oxidation of commercially available, diphenyl(*p*-tolyl)phosphine **1** with potassium permanganate to benzoic acid **2**. (**Scheme 1**) Esterification followed by reduction with borohydride gave the first GAP-anchored benzyl alcohol **4**, or “dppBnOH,” in high yield (Seifert et al., 2016). Similarly, the condensation of diphenylphosphane **5** with 4-chlorobenzonitrile **6**, provided 4-(diphenylphosphanyl)benzonitrile **7**, which upon reduction with LiAlH₄ resulted in amine **8**. Phosphine oxidation of the amine **8** with hydrogen peroxide afforded the second GAP-equipped benzylamine **9** or “dppBnNH₂” (**Scheme 1**) (Hingst et al., 1998; Janssen et al., 2009). The protection of cinnamic acids with dppBnNH₂ was both facile and quantitative compared to dppBnOH. The products **11** and **12** could be easily precipitated from an ethyl acetate/petroleum ether solvent mixture, thereby fulfilling the condition of GAP chemistry. The Bndpp group can be easily regained for reuse either by catalytic hydrogenation or by reduction with borohydride in 10% Pd/C.

We further investigated various reaction parameters by subjecting GAP substrates to aminohalogenation reaction. Initially, the GAP-anchored intermediate **11** was subjected to aminochlorination with dichloramine T (4-TsNCl₂) (1.5 equiv.) in dichloromethane without any catalyst; however, no product was formed after stirring for 48 h. Then iodobenzene diacetate (PhI(OAc)₂) and a series of transition metal catalysts were employed to no avail. Pleasingly, when 1.5 equiv. of tosylamide (4-TsNH₂) was added along with 4-TsNCl₂ (1.5 equiv.) in the presence of catalyst PhI(OAc)₂ (20 mol%), the starting material **11** was consumed in 48 h at room temperature, and a single aminohalogenation product was isolated in a chemical yield of 71% (**Table 1**, entry 9) with a diastereoselective ratio of 8:1. To improve the yield, we again screened a variety of transition-metal compounds such as ZnCl₂, Mn(OAc)₂, Pd(OAc)₂, FeCl₃, and CuI as catalysts for this reaction. The results are depicted in **Table 1**, which specifies that PhI(OAc)₂ (20 mol%) was the potent catalyst for this reaction. It was observed that Mg(OAc)₂ gave no product; Pd(OAc)₂, FeCl₃, and ZnCl₂ gave poor yields, whereas CuI and Cu(OTf)₂ (**Table 1**, entry 14 and 15) gave moderately good yields. The next optimization was the addition of another 0.5 equiv. of each 4-TsNCl₂ and 4-TsNH₂, which increased the yield up to 76% (**Table 1**, entry 16). Refluxing this reaction mixture further enhanced the yield up to 83% (**Table 1**, entry 17). However, the yield decreased to 78% when the reaction was refluxed in the absence of 4 Å molecular sieves (**Table 1**, entry 18).

Using 20 mol% of PhI(OAc)₂ as the catalyst with 2 equiv. of 4-TsNCl₂ and 4-TsNH₂ at reflux temperature, various solvents such as CHCl₃, CH₂Cl₂, MeCN, THF, Et₂O, and toluene were screened, which revealed that CH₂Cl₂ was found to be the best solvent to give **13** in 83% yield with good stereoselectivity (8:1, **Table 2**, entries 1 and 12). Moderate yields were obtained in MeCN and DCE solvents. The product **13** was obtained only with great difficulty in toluene; no reaction was observed in THF, Et₂O, DMF, and MeOH, whereas only traces were formed in dioxane solvent. A decrease in the reaction time by 24 h led to slightly reduced yield (77%) of the product **13** (**Table 2**, entry 11); however, the yield did not change with the prolonged reaction



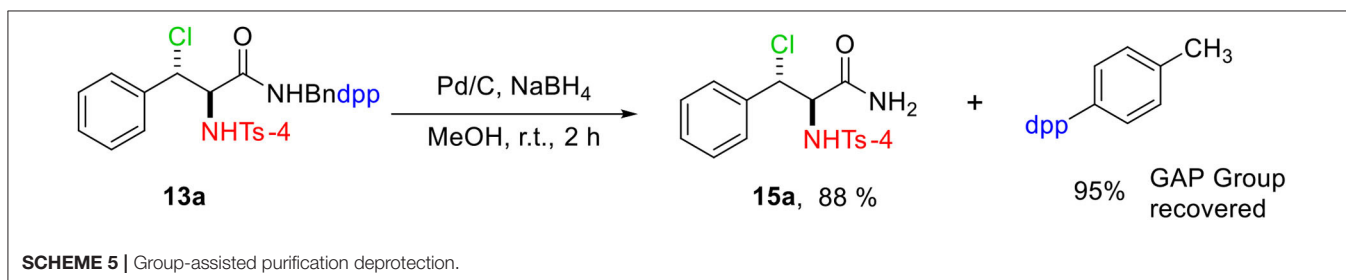
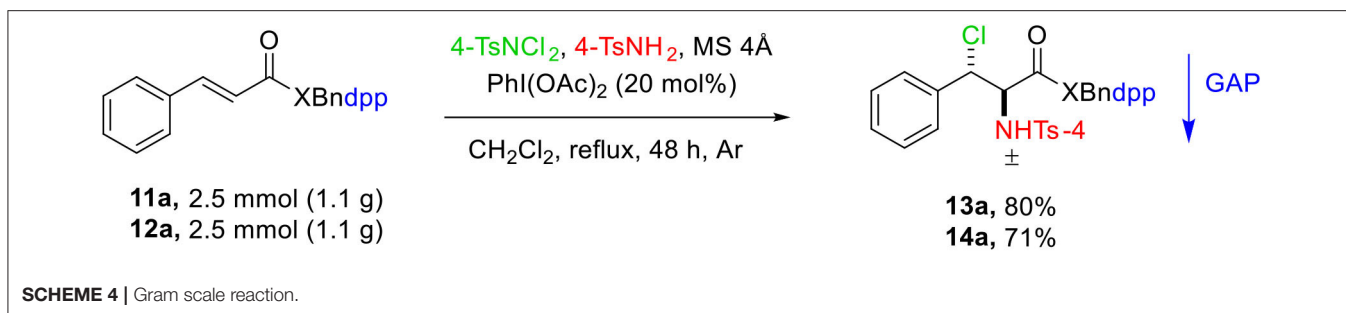
SCHEME 2 | Substrate scope of aminochlorination of *N*-(4-(diphenylphosphoryl)benzyl) cinnamates. Unless otherwise specified, all reactions were performed with 0.15 mmol of **11**, 0.3 mmol of 4-TsNCl₂, 0.3 mmol of 4-TsNH₂, 750 mg of MS 4Å in 1.5 mL of DCM at reflux under Ar. The dr values were determined by the analysis of ¹H and ³¹P NMR spectra. Isolated yields with GAP washing.



time of 72 h (83%, **Table 2**, entry 12). Finally, we noticed that 20 mol% of PhI(OAc)₂ was essential for the reaction as the yield decreased to 27% when 10 mol% of the catalyst was used in the system (**Table 2**, entry 13).

With the optimized reaction parameters, the substrate scope of this reaction was thereafter explored with a variety of GAP auxiliary **4** anchored substituted cinnamic acids **11**. The results are shown in **Scheme 2**. Pleasantly, a wide range of functional groups tolerance was observed on the aromatic ring of cinnamic acids including electron-donating groups **13c–13h** and electron-withdrawing groups **13i–13o**, which provided moderate to high yields (45–94%). As shown in **Scheme 2**, for those substrates

11 bearing electron-donating groups on the aromatic ring of cinnamic acid, the addition reaction went cleanly to produce the relevant adducts **13** in good yields (**Scheme 2**, **13c–13h**). The highest yield of 94% was obtained for **13e** where the aromatic ring has strong electron-donating group MeO at the *ortho*-position. On the other hand, substrates **11** bearing electron-withdrawing groups such as F, Cl, Br, or NO₂ on the aromatic rings gave the resultant products in lower yields under the same conditions (**Scheme 2**, **13i–13o**). The lowest yield of 45% was obtained for **13m**, which has a tertiary butyl group at the *para*-position. Substrates **13n** and **13o** bearing strong electron-withdrawing groups such as NO₂ and Cl did not undergo



reaction, whereas substrate **13p** with *N,N*-dimethylamine group at *para*-position resulted in a complex mixture with traces of desired product.

A major objective of this project was the development of GAP auxiliaries, which could potentially simplify the purification of the haloamine products. Thus, the cinnamic acids **10** were protected with another GAP auxiliary DppBnNH₂ **9** to afford *N*-(4-(diphenylphosphoryl)benzyl) cinnamamides **12**, (**Scheme 1**), which were then exposed to aminochlorination reaction. Conditions for this transformation were also optimized (**Table 1S**, Supporting Information). We found that 20 mol% of PhI(OAc)₂, 2.0 equiv. of 4-TsNH₂ and 4-TsNCl₂, was essential to obtain haloamine product **14a** in 73% yield with diastereoselective ratio of 10:1 when refluxed in dichloromethane for 48 h.

We also investigated the scope of this transformation by using a variety of *N*-(4-(diphenylphosphoryl)benzyl) cinnamamides **12**. As illustrated in **Scheme 3**, the reaction tolerated a wide range of functional groups to provide moderate to high yields (54%–76%). For the substrate having methoxy group at *ortho*-position on aromatic ring, the highest yield of 76% was obtained (**Scheme 3**, **14c**). The nitro group, on the other hand, lowers the yield considerably under the same conditions (**Scheme 3**, **14j**). The substrate with NO₂ group at *ortho*-position of aromatic ring **14k** did not undergo reaction even after 72 h, whereas the reactions for the products **14i** and **14l** were sluggish and resulted in a complex mixture.

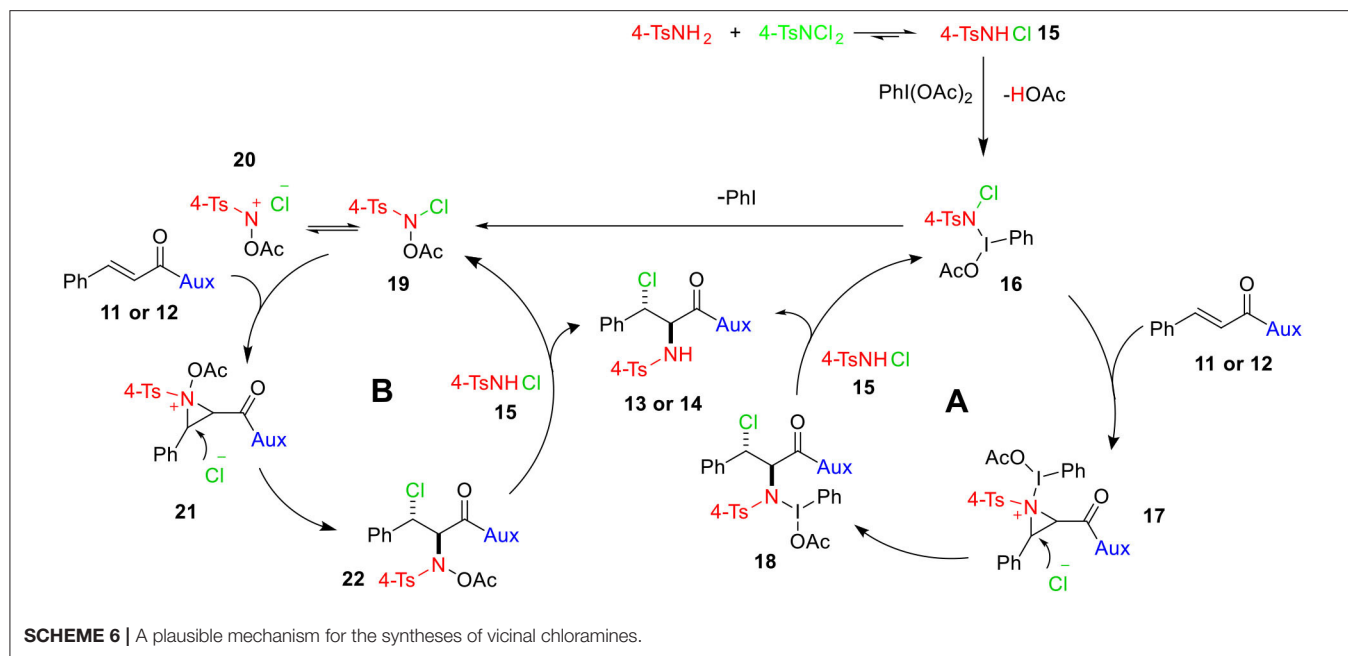
The practicality of this protocol was determined by performing the reaction on gram scale for the starting material **11a** and **12a**, which led to the formation of the products **13a** and **14a** in 80% and 71% yields, respectively (**Scheme 4**).

The GAP-tailored vicinal chloramine was deprotected in the presence of Pd/C and NaBH₄ which afforded Bndpp in 95% yield (**Scheme 5**). For the purification of the products, the mixture

is dissolved in minimal amount of a polar solvent such as ethyl acetate or DCM, and then petroleum ether is added. The GAP auxiliary precipitates in the form of a white solid, which is filtered and washed with petroleum ether. The filtrate is evaporated under vacuum to obtain the desired β-chloroamine as a white product.

MECHANISM

Based on experimental observations and our as well as others' previous works (Li et al., 2001; Wei et al., 2001; Wang and Wu, 2007; Wu and Wang, 2008; Chen et al., 2009), a rational mechanism for the formation of **13** and **14** is illustrated in **Scheme 6**. 4-TsNCl₂ on reaction with 4-TsNH₂ may produce *N*-chloro-*p*-toluenesulfonamide (4-TsNHCl) **15**, which might be oxidized by PhI(OAc)₂ to generate intermediate **16** that may either follow cycle A or cycle B. The intermediate **16**, in cycle A, could form aziridinium **17** with the double bond of **11** or **12**, which in turn is attacked by the dissociated halogen anion from the intermediate **16** at the more electrophilic carbon (beta to carbonyl carbon) to yield compound **18** stereoselectively. Eventually, intermediate **18** together with 4-TsNHCl **15** provides the uttermost haloamine product **13** or **14** and restores intermediate **16**. There is a possibility of formation of *N*-acetoxy-*N*-halo-*p*-toluenesulfonamide **19** when phenyl iodide is released as a result of dissociation of the unstable N-I bond of intermediate **16**, which could then be the active intermediate for cycle B. Species **19** that forms an equilibrium with nitrenium ion intermediate **20** (Kikugawa et al., 2003; Murata et al., 2008) could react with olefin **11** or **12** to afford aziridinium intermediate **21**, which would lead to intermediate **22** following an S_N2 nucleophilic attack by the nearby halide anion. Finally, the reaction of the intermediate



22 with 4-TsNHCl gives the final product and regenerate intermediate 19.

EXPERIMENTAL SECTION

Aminochlorination of 4-(Diphenylphosphoryl)Benzyl Cinnamates 13 and *N*-(4-(Diphenylphosphoryl)Benzyl) Cinnamamides 14

Typical procedure: Into a dry vial, 11 or 12 (1.5 mmol, 1 eq), 4-TsNCl₂ (3 mmol, 2 eq) 4-TsNH₂ (3 mmol, 2 eq), PhI(OAc)₂ (20 mol%), and freshly activated 4 Å molecular sieves (150 mg) were added. The resulting mixture was capped under argon protection. Anhydrous DCM (3 mL) was injected through a syringe and was refluxed for 48 h. After completion (monitored by TLC), the reaction was quenched with saturated aqueous Na₂SO₃ 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 evaporated to dryness *in vacuo*. The mixture is dissolved in minimal amount of a polar solvent such as ethyl acetate or DCM, and then petroleum ether is added. The GAP auxiliary precipitates in the form of a white solid, which is filtered and washed with petroleum ether. The filtrate is evaporated under vacuum to obtain the desired β-chloroamine as a white product.

General Procedure for Deprotection of GAP Auxiliary BnDpp

To a stirred solution of 13a or 14a (0.1 g, 0.16 mmol) and 10 wt% Pd/C (10 mg) in MeOH (1 mL), NaBH₄ (7.6 mg, 2 equiv.) was added. The 10-mL flask was closed with a rubber septum with an empty (deflated) balloon to avoid the loss of generated hydrogen and overpressure in the flask. After 2 h, the reaction

mixture was filtered through Celite, and filtrate was evaporated to dryness and redissolved in EtOAc. Then, the reaction mixture was neutralized with KHSO₄. The organic layer was separated, dried over anhydrous Na₂SO₄, and evaporated to dryness to afford crude GAP auxiliary, which was easily purified using the GAP washing method.

CONCLUSION

A highly efficient regioselective and stereoselective aminochlorination reaction of electron-deficient olefins anchored with GAP auxiliaries dppBnOH and dppBnNH₂ catalyzed by PhI(OAc)₂ in dichloromethane with 4-TsNH₂ and 4-TsNCl₂ as the nitrogen and chlorine sources has been developed. Moderate to good chemical yields and excellent regioselectivity and stereoselectivity have been obtained. The GAP approach has been effectively implemented, which bypasses column chromatography and recrystallization. Pure products have been obtained simply by washing the crude mixtures with inexpensive petroleum solvents or cosolvents to give good to high yields. Besides, the GAP auxiliary is recyclable and reusable.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

GL and AR designed the project. AR, NZ, and WY performed the experiments. AA and PZ analyzed the data. AR, AA, and GL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fchem.2020.00523/full#supplementary-material>

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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