JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

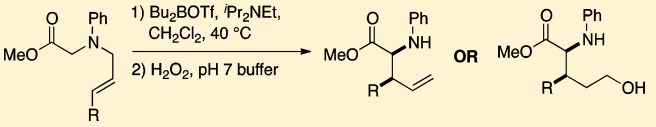
# Aza-Wittig Rearrangements of *N*-Benzyl and *N*-Allyl Glycine Methyl Esters. Discovery of a Surprising Cascade Aza-Wittig Rearrangement/Hydroboration Reaction

Renata K. Everett and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 N. University Avenue, Ann Arbor, Michigan 48109-1055, United States

Supporting Information

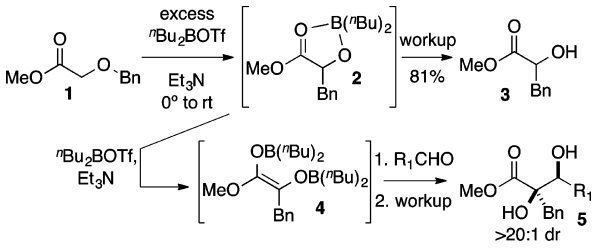
**ABSTRACT:** Treatment of *N*-(arylmethyl)-*N*-aryl or *N*-allyl-*N*-aryl glycine methyl ester derivatives with $^{n}Bu_2BOTf$ and $^{i}Pr_2NEt$ effects an aza-Wittig rearrangement that provides *N*-aryl phenylalanine methyl ester derivatives and *N*-aryl allylglycine methyl ester derivatives, respectively, in good yield with moderate to good diastereoselectivity. Under similar conditions, analogous substrates bearing *N*-carbonyl groups are converted to 1,4,2-oxazaborole derivatives. Additionally, *N*-allyl-*N*-aryl glycine methyl ester derivatives subjected to similar conditions at elevated temperatures undergo an aza-[2,3]-Wittig rearrangement, followed by a subsequent hydroboration oxidation reaction, to afford substituted amino alcohol products.




## INTRODUCTION

Wittig rearrangements of $\alpha$-alkoxy carbanions have been well documented over the past 70 years[1,2] and are useful synthetic methods for carbon−carbon bond formation. Our group has previously reported a tandem Wittig rearrangement/aldol reaction sequence, which affords substituted $\alpha,\beta$-dihydroxy esters in good yield and high diastereoselectivity under mild conditions by way of intermediate boron enolates (Scheme 1).[3] With the use of 2-phenylcyclohexanol as a chiral auxiliary, these reactions can be performed asymmetrically, yielding the diol products in up to 95% ee after auxiliary cleavage.[4] Furthermore, analogous tandem Wittig rearrangement/Mannich reactions provide access to the corresponding amino alcohols with excellent stereocontrol.[5] Given the synthetic utility of these transformations, we sought to expand the scope of these processes to allow for the construction of other useful building blocks. We hypothesized that the corresponding enolate aza-Wittig rearrangement could be achieved under similar conditions from an appropriately substituted $\alpha$-amino ester.[6] The rearrangement itself would provide access to unnatural amino acid derivatives, and if coupled with a subsequent aldol reaction, could produce biologically interesting $\beta$-hydroxy-$\alpha$-amino acid derivatives.

**Scheme 1. Tandem Wittig Rearrangement/Aldol Reaction**




Though Wittig rearrangements of $\alpha$-alkoxy carbanions are well documented, analogous transformations of $\alpha$-amino anions have been less explored.[7] Aza-[1,2]-Wittig rearrangements are very rare and have most frequently been observed as side reactions in aza-[2,3]-Wittig rearrangements;[8,9] the migration of benzyl groups in synthetically useful yields (>60%) has only been reported on a single occasion.[9] Aza-[2,3]-Wittig rearrangements of $\alpha$-amino esters can be induced under classical basic conditions via intermediate enolates, but these conditions are generally only effective with strained ring amine substrates (such as aziridines)[10] or with substrates that bear a trialkylsilyl group on the alkene.[11] Aza-[2,3]-Wittig rearrangements of unactivated $\alpha$-amino ester or amide substrates have been described, but these transformations typically require either in situ quaternization of the amino group through alkylation[12] or use of both a base and a strong Lewis acid,[13] which leads to the generation of ammonium ylides that undergo rearrangement more readily than amines.[14]

## RESULTS AND DISCUSSION

**Preliminary Studies on Aza-[1,2]-Wittig Rearrangements—Unexpected Generation of 1,4,2-Oxazaborole Derivatives.** Considering the scarcity of successful aza-[1,2]-Wittig rearrangements, we elected to begin our initial studies by focusing on the development of reaction conditions for the aza-[1,2]-Wittig rearrangement of *N*-benzyl glycine ester derivatives (rather than the tandem rearrangement/aldol sequence). To this end, *N*-benzyl-*N*-boc-glycine methyl ester **6a** was selected as our first substrate, since prior studies on aza-[2,3]-Wittig rearrangements have shown that electron-withdrawing *N*-substituents improve reactivity. This substrate was prepared in two steps through alkylation of benzylamine with methyl 2-bromoacetate,

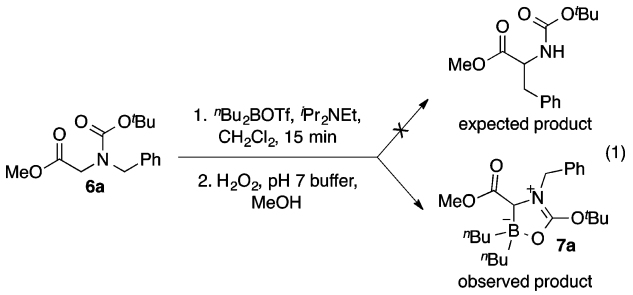
**Received:** June 8, 2015
**Published:** September 1, 2015





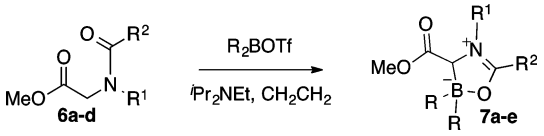
DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

followed by boc-protection of the resulting secondary amine. Surprisingly, as illustrated in eq 1, when **6a** was subjected to the reaction conditions we have previously employed in [1,2]-Wittig rearrangements of **1**, no rearrangement occurred. Instead, 1,4,2-oxazaborole derivative **7a** was formed.[15]




In an effort to circumvent this unusual transformation and instead facilitate the desired [1,2]-Wittig rearrangement, we examined the reactivity of other *N*-benzyl glycine methyl ester derivatives bearing amide protecting groups. However, substrates with *N*-pivalolyl or *N*-acetyl groups were also transformed to oxazaboroles (Table 1), and efforts to induce

**Table 1. Formation of 1,4,2-Oxazaborole Derivatives**[a]

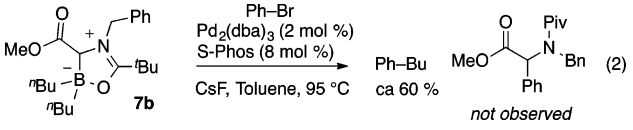



| entry | $R^1$ | $R^2$ | $R_2BOTf$ | yield[b] |
|---|---|---|---|---|
| 1 | Bn | O$^t$Bu (**6a**) | $^n$Bu$_2$BOTf | 40% (**7a**) |
| 2 | Bn | $^t$Bu (**6b**) | $^n$Bu$_2$BOTf | 87% (**7b**) |
| 3 | Bn | $CH_3$ (**6c**) | $^n$Bu$_2$BOTf | 48% (**7c**) |
| 4 | Allyl | O$^t$Bu (**6d**) | $^n$Bu$_2$BOTf | 66% (**7d**) |
| 5 | Bn | $^t$Bu (**6b**) | 9-BBNOTf | 90% (**7e**) |

[a]Conditions: (i) 1.0 equiv of **6**, 3.2 equiv of $R_2BOTf$, 4.0 equiv of $^i$Pr$_2$NEt, $CH_2Cl_2$, 0.25 M, 15 min, 0 °C to rt. (ii) $H_2O_2$, pH 7 buffer, MeOH, 1 h, 0 °C to rt. [b]Isolated yield, average of two or more experiments.

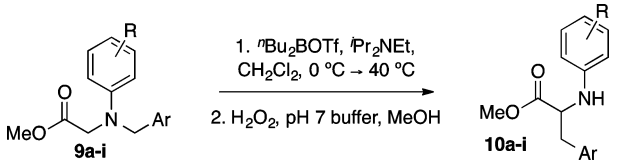
[2,3]-Wittig rearrangement of a substrate that contained an *N*-allyl group (**6d**) also led to oxazaborole formation (Table 1, entry 4). Use of 9-BBNOTf in place of $^n$Bu$_2$BOTf failed to alter the course of these reactions (Table 1, entry 5).

The oxazaborole derivatives **7a**–**7e** proved to be surprisingly unreactive. For example, heating **7b** to 135 °C in xylenes did not lead to any rearranged product; unreacted starting material was recovered. Moreover, these compounds also failed to react with acids, bases, and oxidants such as alkaline hydrogen peroxide. The structure of **7e** was confirmed via X-ray crystallography, which clearly revealed the presence of a boron–oxygen bond. It seems likely that the high stability of these compounds is a result of this B–O bond, which renders the boron atom tetravalent and anionic, rather than open-shell and reactive. We briefly attempted to conduct Suzuki coupling reactions between **7b** and 4-bromotoluene, as organoborates are known to undergo transmetalation with arylpalladium(II) complexes.[16] However, these conditions also led to no reaction (eq 2).




**Aza-[1,2]-Wittig Rearrangements of *N*-Aryl-*N*-Benzyl Glycine Methyl Ester Derivatives.** Our initial studies suggested that the failure of substrates **6** to undergo rearrangement may be due to the propensity of the carbonyl moiety of an amide or carbamate protecting group to interact with the boron atom after enolate generation. As such, it seemed likely that use of glycine *N*-substituents that lack carbonyl functional groups could lead to successful rearrangement. Thus, *N*-benzyl glycine methyl esters bearing *N*-alkyl, *N*-phosphoryl, and *N*-tosyl groups were examined, but efforts to effect rearrangements of these substrates were also unsuccessful. However, we were gratified to find that the desired [1,2] rearrangement could be achieved with the use of substrate **9a**, which contains an *N*-phenyl group. Further experimentation revealed that, by extending the reaction time and increasing the temperature, the desired amine **10a** could be isolated in 64% yield (Table 2,

**Table 2. Aza-[1,2]-Wittig Rearrangement**[a]




| entry | R | Ar | yield[b] |
|---|---|---|---|
| 1 | H (**9a**) | Ph | 64% (**10a**) |
| 2 | *p*-Br (**9b**) | Ph | 54% (**10b**) |
| 3 | *p*-OMe (**9c**) | Ph | 65% (**10c**) |
| 4 | *p*-$CF_3$ (**9d**) | Ph | 24% (**10d**) |
| 5 | H (**9e**) | *p*-BrPh | 67% (**10e**) |
| 6 | H (**9f**) | *o*-BrPh | 53% (**10f**) |
| 7 | H (**9g**) | 2-furyl | 68% (**10g**) |
| 8 | H (**9h**) | 2-thiophenyl | 66% (**10h**) |
| 9 | H (**9i**) | *N*-Ts-2-pyrrolyl | 54% (**10i**) |

[a]Conditions: (i) 1.0 equiv of **9**, 3.2 equiv of $^n$Bu$_2$BOTf, 4.0 equiv of $^i$Pr$_2$NEt, $CH_2Cl_2$, 0.25 M, 0–40 °C. (ii) $H_2O_2$, pH 7 buffer, MeOH. [b]Isolated yield, average of two or more experiments.

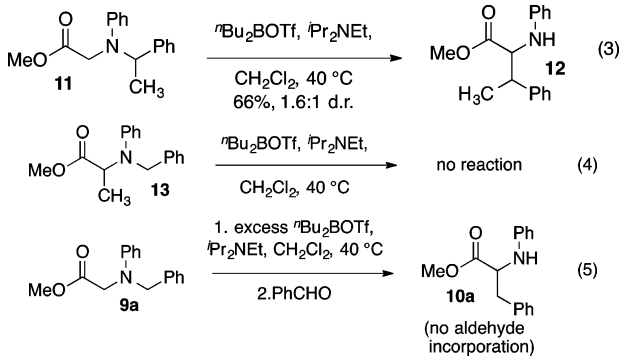
entry 1). When a single equivalent of dibutylboron triflate was used, the rearrangement reaction proceeded to 74% conversion (26% unreacted starting material), as judged by $^1$H NMR analysis. This latter experiment suggests that the reaction proceeds through a boron enolate that contains a single equivalent of an organoboron species, rather than an intermediate that bears two dialkylboron units (one bound to oxygen and one bound to nitrogen).[17]

Once satisfactory reaction conditions had been determined, additional substrates were prepared in order to examine the scope of the transformation. These new substrates were generated in three steps from substituted anilines and benzaldehyde derivatives via imine formation, reduction, and *N*-alkylation with methyl 2-bromoacetate. As shown in Table 2, substitution on both the *N*-aryl group and the benzyl group was tolerated. Additionally, substrates bearing heteroaromatic groups such as 2-furyl, 2-thiophenyl, or *N*-tosyl-2-pyrrolyl underwent the [1,2] rearrangement in good yield (Table 2, entries 7–9). However, we were unable to examine the reactivity of the corresponding NH or *N*-alkylpyrrole derivatives analogous to **9i**, as these compounds were unstable and rapidly decomposed upon isolation. In addition, due to a combination of slow reaction rate and product decomposition as a result of the extended reaction time, the rearrangement of **9d**, which contains an *N*-*p*-trifluoromethylphenyl group, proceeded in poor yield.



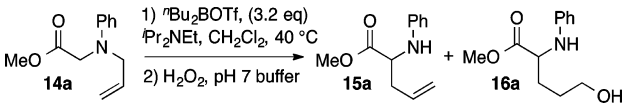
DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041–9056

The scope and stereocontrol of the glycine ester aza-[1,2]-Wittig rearrangement was explored by preparing substrates **11** and **13**, which bear a methyl group at the benzylic position or adjacent to the ester, respectively. The rearrangement of **11** to **12** proceeded in good yield, though the diastereoselectivity of this reaction was low (eq 3). The diastereoselectivity was not improved with the use of 9-BBN-OTf in place of $^{n}Bu_2BOTf$; a similar mixture of diastereomers was obtained under these conditions. Though substitution at the benzylic position was tolerated (eq 3), substrate **13** proved to be unreactive toward our standard conditions (eq 4). It is possible that the lack of reactivity of **13** is due either to difficulty generating the requisite boron enolate from the more sterically encumbered substrate or that the rearrangement of the more hindered enolate is simply slow. However, our subsequent studies on aza-[2,3]-rearrangements of analogous substrates suggest that the enolate is likely generated, but fails to rearrange (see below). We also observed that no aldol product was generated when **9a** was treated with excess $^{n}Bu_2BOTf/^{i}Pr_2NEt$, followed by addition of an aldehyde to the reaction mixture (eq 5), unlike the reactivity that was previously observed in reactions of **1** (Scheme 1). As above, the failed aldol reaction likely is a result of the steric hindrance of the enolate derived from **10a**.[18]




**Aza-[2,3]-Wittig Rearrangements of *N*-Allyl-*N*-Aryl Glycine Methyl Ester Derivatives.** Having successfully developed conditions for aza-[1,2]-Wittig rearrangements of glycine methyl ester derivatives via their boron enolates, we sought to explore the feasibility of the analogous boron enolate aza-[2,3]-Wittig rearrangements. To this end, *N*-allyl-*N*-phenyl glycine methyl ester **14a** was prepared in one step via alkylation of *N*-allylaniline with methyl 2-bromoacetate. We then subjected **14a** to our standard reaction conditions and were surprised to discover that a mixture of two products was formed (Scheme 2). Both products appear to be the consequence of a

**Scheme 2. Initial Results of Aza-[2,3]-Wittig Rearrangement**




[2,3] rearrangement, but **16a** results from subsequent alkene hydroboration/oxidation. Although the reaction conditions described above do not employ a standard borohydride source for the alkene hydroboration step, it appears likely that an alkyl borohydride reagent is formed under the reaction conditions through $\beta$-hydride elimination of the dibutylboron triflate reagent at the elevated reaction temperatures.[19]

Efforts to reproduce this result led to variable mixtures of **15a** and **16a**, but given the likelihood that the requisite alkylborohydride is generated by thermal decomposition of dibutylboron triflate, it seemed plausible that temperature could have an impact on product distribution. Further experimentation revealed that the inconsistent results were predominantly due to fluctuations in oil bath temperature during the course of the reaction. By lowering the reaction temperature to 35 °C with better control of bath temperature, and also reducing the amount of $^{n}Bu_2BOTf$ to 1.5 equiv, the competing postrearrangement hydroboration was minimized, and **15a** was isolated as the sole product in 70% yield (Table 3, entry 1).

To explore the scope of the [2,3] rearrangements, we prepared several *N*-allyl-*N*-phenylglycine substrates in a manner analogous to the synthesis of **9a–i**. When subjected to the optimized reaction conditions, a variety of substrates cleanly underwent [2,3] rearrangement, as shown in Table 3. Terminal and internal substitution on the alkene was tolerated as well as substitution on the *N*-aryl group. Substrates bearing internal alkenes underwent diastereoselective rearrangement to provide products with 5:1 to 8:1 dr in most cases. However, substrate **14c** rearranged in much higher dr (>20:1), and selectivity was low with cyclohexene derived substrate **14h** (2:1 dr).[20] Two substrates, **14c** and **14d**, yielded a mixture of [1,2] and [2,3] rearrangement products (Table 3, entries 3 and 4), as has been observed in other Wittig rearrangements of allylic compounds.[21]

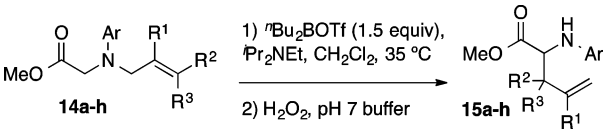
**One-Pot Sequential Aza-[2,3]-Wittig Rearrangement/Hydroboration/Oxidation Reactions.** Given the potential synthetic utility of 1,4-amino alcohol products such as **16a**, which was formed as a side product in our initial efforts to induce aza-[2,3]-Wittig rearrangement of **14** (Scheme 2), we sought to optimize this tandem rearrangement/hydroboration/oxidation sequence. Further experimentation revealed that higher temperatures, longer reaction times, and a larger excess of $^{n}Bu_2BOTf$ (4 equiv) favor the subsequent hydroboration reaction, but complete conversion of **15a** to **16a** in the one-flask transformation was difficult to achieve. Optimal results were attained when a second portion of $^{n}Bu_2BOTf$ was added to the reaction vessel after 2 h of reaction time; this protocol led to the formation of **16a** in 52% isolated yield (Table 4, entry 1). Despite this improvement, unreacted **15a** made up the majority of the mass balance in these reactions. In cases where competing reaction pathways resulted in two products, only the [2,3] rearrangement product, which bears a terminal alkene, was observed to undergo the subsequent hydroboration/oxidation (Table 4, entries 3 and 4).

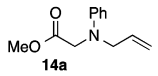
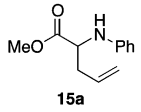
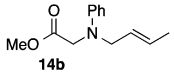
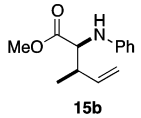
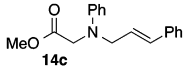
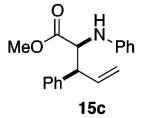
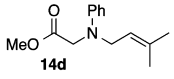
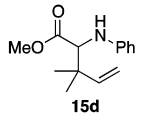
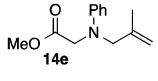
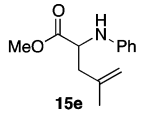
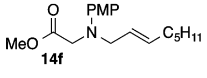
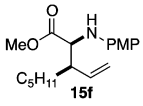
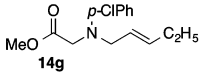
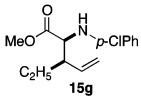
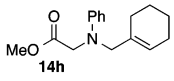
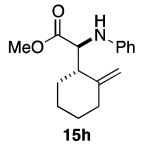
To further explore the scope and limitations of this transformation, compound **17**, which contains a methyl group adjacent to the ester moiety, was prepared. As observed previously (eq 3), the [2,3]-rearrangement did not occur. However, in this case, the methyl ester was hydrolyzed, presumably via elimination of the boron enolate under thermal conditions,[22] leading to a ketene intermediate **19** that can be captured by water during the aqueous workup to form the observed carboxylic acid, **20** (Scheme 3). As observed in [1,2]-Wittig rearrangements of *N*-benzyl glycine derivatives, no aldol product was generated when **14a** was treated with excess $^{n}Bu_2BOTf/^{i}Pr_2NEt$, followed by addition of an aldehyde to the reaction mixture.

**Efforts to Achieve Asymmetric Aza-Wittig Rearrangements of Glycine Ester Derivatives.** In order to probe the feasibility of enantioselective aza-Wittig rearrangements of glycine methyl ester derivatives,[11c,13b] we have conducted preliminary studies on transformations of **21a** and **21b**. We have


DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041–9056

**Table 3. Aza-[2,3]-Wittig Rearrangement**[a]

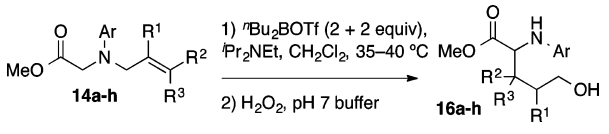


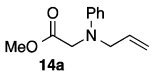
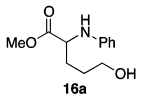
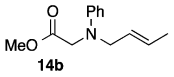
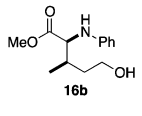
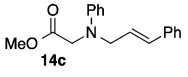
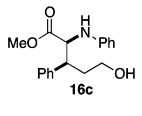
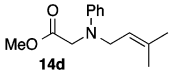
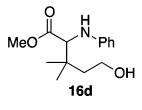
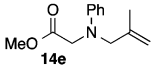
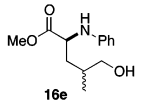
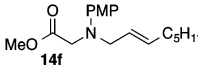
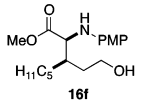
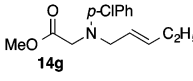
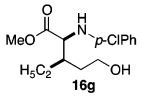
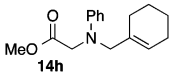
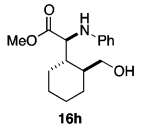

| entry | substrate | product | yield[b] |
|---|---|---|---|
| 1 |  |  | 70% |
| 2 |  |  | 60% (7:1 dr) |
| 3 |  |  | 73%[c] (>20:1 dr) |
| 4 |  |  | 75%[d] |
| 5 |  |  | 55% |
| 6 |  |  | 58% (5:1 dr) |
| 7 |  |  | 62% (8:1 dr) |
| 8 |  |  | 56% (2:1 dr) |

[a]Conditions: (i) 1.0 equiv of **6**, 1.5 equiv of $^{n}Bu_2BOTf$, 1.7 equiv of $^{i}Pr_2NEt$, $CH_2Cl_2$, 0.25 M, 4 h, 0−35 °C. (ii) $H_2O_2$, pH 7 buffer, MeOH, 1 h, 0 °C to rt. [b]Isolated yield, average of two or more experiments. [c]A 4:1 mixture of [2,3] and [1,2] rearrangement products was obtained. [d]A 2:1 mixture of [2,3] and [1,2] rearrangement products was obtained.

previously demonstrated that 2-phenylcyclohexanol functions efficiently as a chiral auxiliary in tandem asymmetric Wittig rearrangement/aldol reactions of glycolate esters (up to 95% ee after auxiliary cleavage).[4] Thus, substrates **21a** and **21b**, bearing this chiral auxiliary, were synthesized and subjected to the standard reaction conditions. Unfortunately, although the chemical yields of the rearrangements were good, the diastereoselectivity in each case was modest (Table 5). Nonetheless, these experiments illustrate the possibility of achieving asymmetric induction, although further optimization is clearly needed.

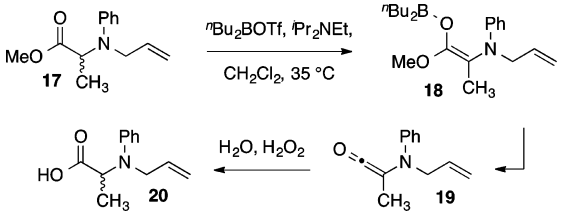
**Table 4. Aza-[2,3]-Wittig Rearrangement/Hydroboration**[a]




| entry | substrate | product | yield[b] |
|---|---|---|---|
| 1 |  |  | 52% |
| 2 |  |  | 54% (10:1 dr) |
| 3 |  |  | 57% (>20:1 dr) |
| 4 |  |  | 51% |
| 5 |  |  | 41% (1:1 dr) |
| 6 |  |  | 44% (9:1 dr) |
| 7 |  |  | 48% (13:1 dr) |
| 8 |  |  | 38% (3:1 dr) |

[a]Conditions: (i) 1.0 equiv of **14**, 2.0 equiv of $^{n}Bu_2BOTf$, 4.0 equiv of $^{i}Pr_2NEt$, $CH_2Cl_2$, 0.25 M, 2 h, 0−35 °C. (ii) 2.0 equiv of $^{n}Bu_2BOTf$, 4 h, 0−40 °C. (iii) $H_2O_2$, pH 7 buffer, MeOH, 1 h, 0 °C to rt. [b]Isolated yield, average of two or more experiments.

**Scheme 3**



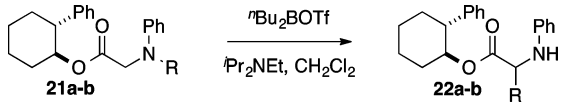

## CONCLUSION

In conclusion, we have developed a new aza-[1,2]-Wittig rearrangement of *N*-aryl-*N*-benzyl glycine methyl esters. These transformations constitute rare examples of benzyl group migration in aza-Wittig rearrangements and provide a concise four-step approach to the construction of substituted *N*-aryl phenylalanine derivatives. We have also illustrated that the



DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

**Table 5. Asymmetric Aza-Wittig Rearrangement**




| entry | R | yield[c] | dr |
|---|---|---|---|
| 1 | benzyl[a] (**21a**) | 85% (**22a**) | 1.6:1 |
| 2 | allyl[b] (**21b**) | 64% (**22b**) | 1.3:1 |

[a]Conditions: (i) 1.0 equiv of **21a**, 3.2 equiv of $^n$Bu$_2$BOTf, 4.0 equiv of $^i$Pr$_2$NEt, CH$_2$Cl$_2$, 0.25 M, 2 h, 0−40 °C. (ii) H$_2$O$_2$, pH 7 buffer, MeOH, 1 h, 0 °C to rt. [b]Conditions: (i) 1.0 equiv of **21b**, 1.5 equiv of $^n$Bu$_2$BOTf, 1.7 equiv of $^i$Pr$_2$NEt, CH$_2$Cl$_2$, 0.25 M, 4 h, 0−35 °C. (ii) H$_2$O$_2$, pH 7 buffer, MeOH, 1 h, 0 °C to rt. [c]Isolated yield.

analogous boron-mediated aza-[2,3]-Wittig rearrangements of *N*-aryl-*N*-allyl glycine methyl esters afford γ,δ-unsaturated amino esters in moderate to good yield and diastereoselectivity. Moreover, we have discovered an unusual cascade aza-[2,3]-Wittig rearrangement/hydroboration sequence that occurs under slightly modified conditions to afford 4-hydroxy amino esters. These studies illustrate that aza-Wittig rearrangements can be induced under relatively mild conditions, without the need for activated substrates, extremely strong Lewis acids such as BF$_3$, or quaternary ammonium salt generation.

## EXPERIMENTAL SECTION

**General Considerations.** All reactions were carried out under a nitrogen atmosphere in flame-dried glassware. All reagents were obtained from commercial sources and were used as obtained unless otherwise noted. Dichloromethane was purified using a GlassContour solvent purification system. Hünig's base was distilled from CaH$_2$. All compounds previously reported in the literature were characterized (with respect to identity and purity) by $^1$H NMR analysis unless otherwise noted. Yields refer to isolated yields of compounds estimated to be ≥95% pure, as determined by $^1$H NMR analysis unless otherwise noted. The yields reported in the Supporting Information describe the result of a single experiment, whereas yields reported in Tables 1−5 and eqs 1−4 are average yields of two or more experiments. Thus, the yields reported in the Supporting Information may differ from those shown in Tables 1−5 and eqs 1−4. The majority of the $^1$H NMR spectra were processed using vnmrJ software, whereas spectra containing expanded regions were processed with MestReNova. Thus, the appearance of spectra may differ slightly depending on the processing software.

**Handling of Dialkylboron Reagents.** Dibutylboron triflate (1.0 M solution in methylene chloride) and 9-BBN-OTf (0.5 M solution in hexanes) were obtained from Aldrich Chemical Co. and used as obtained. Because of the air and moisture sensitivity of these reagents, they must be stored and transferred under a rigorously maintained nitrogen atmosphere.

**Synthesis of Glycine Methyl Ester Derived Substrates.** *Methyl 2-(Benzylamino)acetate.* A flame-dried flask was cooled under a stream of nitrogen and charged with benzylamine (2.36 mL, 21.6 mmol) in THF (10 mL, 1 M). This solution was cooled to 0 °C before methyl bromoacetate (0.93 mL, 9.8 mmol) was added dropwise. The mixture was allowed to warm to rt over 2.5 h, at which point the starting material had been completely consumed, as judged by TLC analysis. The mixture was concentrated *in vacuo*, and the resulting residue was dissolved in Et$_2$O and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by flash chromatography on silica gel with 60% hexanes/ethyl acetate as the eluent to afford 1.12 g (63%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[23] $^1$H NMR (500 MHz, CDCl$_3$) δ 7.30 (d, *J* = 4.3 Hz, 4 H), 7.29−7.24 (m, 1 H), 3.81 (s, 2 H), 3.73 (s, 3 H), 3.43 (s, 2 H), 1.93 (s, br, 1 H).

*Methyl 2-[Benzyl(tert-butoxycarbonyl)amino]acetate (**6a**).* A flame-dried flask was cooled under a stream of nitrogen and charged with methyl 2-(benzylamino)acetate (400 mg, 2.23 mmol), dichloromethane (11 mL, 0.2 M), Boc$_2$O (536 mg, 2.46 mmol), and triethylamine (0.94, 6.70 mmol). The resulting solution was stirred at rt overnight and then concentrated *in vacuo*. The crude product was purified by flash chromatography with 80% hexanes/ethyl acetate as the eluent to afford 618 mg (99%) of the title compound as a colorless oil. The compound was determined to exist as a 1:1 mixture of rotamers by NMR analysis. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.35−7.21 (m, 5 H), 4.56 (s, 1 H), 4.52 (s, 1 H), 3.93 (s, 1 H), 3.79 (s, 1 H), 3.70 (m, 3 H), 1.47 (m, 9 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 170.4, 155.8, 155.6, 137.5, 137.3, 128.6, 128.1, 127.5, 127.4, 80.7, 80.5, 52.0, 51.9, 51.5, 51.0, 47.9, 47.5, 28.3, 28.2 (three carbon signals are missing due to incidental equivalence); IR (neat, ATR) 1749, 1690 cm$^{-1}$. HRMS (ESI+, magnetic sector) *m*/*z*: [M + Na]$^+$ calcd for C$_{15}$H$_{21}$NO$_4$Na 302.1368; Found 302.1363.

*Methyl 2-(N-Benzylpivalamido)acetate (**6b**).* A flame-dried flask was cooled under a stream of nitrogen and charged with methyl 2-(benzylamino)acetate (400 mg, 2.23 mmol), pyridine (5.6 mL, 0.4 M), and pivaloyl chloride (0.5 mL, 3.78 mmol). The resulting solution was stirred at rt for 1 h and then concentrated *in vacuo*. The resulting material was dissolved in Et$_2$O, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography with 80% hexanes/ethyl acetate as the eluent to afford 495 mg (84%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38−7.26 (m, 3 H), 7.21 (d, *J* = 7.2 Hz, 2 H), 4.83 (s, 2 H), 3.91 (s, 2 H), 3.71 (s, 3 H), 1.35 (s, 9 H); $^{13}$C NMR (176 MHz, CDCl$_3$) δ 170.1, 128.8, 127.7, 126.9, 52.0, 48.4, 38.9, 28.4, 27.1 (two carbon signals are missing due to incidental equivalence); IR (neat, ATR) 1748, 1634 cm$^{-1}$. HRMS (ESI+, magnetic sector) *m*/*z*: [M + H]$^+$ calcd for C$_{15}$H$_{22}$NO$_3$ 264.1600; Found 264.1596.

*Methyl 2-(N-Benzylacetamido)acetate (**6c**).*[24] A flame-dried flask was cooled under a stream of nitrogen and charged with methyl 2-(benzylamino)acetate (370 mg, 2.06 mmol), DCM (4.1 mL, 0.5 M), acetyl chloride (0.22 mL, 3.09 mmol), and triethylamine (0.43 mL, 3.09 mmol). The resulting solution was stirred at rt for 14 h and then was poured into water. The layers were separated, and the organic layer was extracted twice with DCM. The combined organic layers were washed with water and then brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography with 80% hexanes/ethyl acetate as the eluent to afford 236 mg (52%) of the title compound as a colorless oil. The compound was determined to exist as a 2.4:1 mixture of mixture of rotamers, with spectroscopic properties identical to those previously reported.[24] $^1$H NMR (700 MHz, CDCl$_3$) δ 7.36 (t, *J* = 7.6 Hz, 1.4 H), 7.34−7.23 (m, 1.6 H), 7.24−7.20 (m, 0.6 H), 7.21−7.16 (m, 1.4 H), 4.63 (s, 0.6 H), 4.61 (s, 1.4 H), 4.05 (s, 1.4 H), 3.91 (s, 0.6 H), 3.70 (s, 3 H), 2.21 (s, 2.15 H), 2.11 (s, 0.85 H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 171.4, 171.0, 169.7, 169.5, 136.6, 136.0, 128.9, 128.6, 128.4, 127.8, 127.6, 126.6, 52.9, 52.3, 52.0, 49.4, 49.0, 46.8, 21.4, 21.2.

*Methyl N-Allylglycinate.*[25] A flame-dried flask was cooled under a stream of nitrogen and charged with allylamine (2.16 mL, 18.8 mmol) in THF (13 mL, 1 M). This solution was cooled to 0 °C before methyl bromoacetate (1.24 mL, 13.0 mmol) was added dropwise. The mixture was allowed to warm to rt over 2.5 h, at which point the starting material had been completely consumed, as judged by TLC analysis. The mixture was concentrated *in vacuo*, and the resulting residue was dissolved in Et$_2$O and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by flash chromatography with 60% hexanes/ethyl acetate as the eluent to afford 1.28 g (75%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[25] $^1$H NMR (400 MHz, CDCl$_3$) δ 5.89−5.79 (m, 1 H), 5.20−5.08 (m, 2 H), 3.71 (s, 3 H), 3.39 (s, 2 H), 3.24 (dd, *J* = 6.1, 1.2 Hz, 2 H), 1.64 (s, br, 1 H).

*Methyl-N-allyl-N-(tert-butoxycarbonyl)glycinate (**6d**).*[26] A flame-dried flask was cooled under a stream of nitrogen and charged with methyl *N*-allylglycinate (98 mg, 0.76 mmol), dichloromethane (4 mL, 0.2 M), Boc$_2$O (183 mg, 0.84 mmol), and triethylamine (0.32 mL, 2.28 mmol). The resulting solution was stirred at rt overnight and then concentrated *in vacuo*. The crude product was purified by flash


DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

chromatography with 80% hexanes/ethyl acetate as the eluent to afford 170 mg (98%) of the title compound as a colorless oil. The product was determined to exist as a 1:1 mixture of rotamers and displayed spectroscopic properties identical to those previously reported.[26] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.84−5.73 (m, 1 H), 5.18−5.10 (m, 2 H), 3.96−3.84 (m, 4 H), 3.73 (s, 3 H), 1.47−1.43 (m, 9 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 170.6, 133.7, 133.6, 117.6, 116.8, 80.4, 51.9, 51.8, 50.7, 50,2, 47.9, 47.5, 28.3, 28.2 (four carbon signals are missing due to incidental equivalence).

**Synthesis of 1,2,4-Oxazaborole Derivatives.** *General Procedure 1.* An oven-dried flask was evacuated and backfilled with nitrogen three times and then charged with a 1 M solution of dialkylboron triflate in methylene chloride (3.2 equiv). The solution was cooled to 0 °C, and $^i$Pr$_2$NEt (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in dichloromethane was then added, and the resulting solution was warmed to rt. After stirring for 15 min, the mixture was cooled to 0 °C, opened to air, diluted with diethyl ether, and quenched by the addition of water. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted twice with $Et_2O$. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5−10% ethyl acetate in hexanes as the eluent.

*4-Benzyl-5-(tert-butoxy)-2,2-dibutyl-3-(methoxycarbonyl)-2,3-dihydro-1,4,2-oxazaborol-4-ium-2-uide (**7a**).* General procedure 1 was employed for the transformation of **6a** (84 mg, 0.3 mmol) using 1 M dibutylboron triflate solution in dichloromethane (0.96 mL, 0.96 mmol) and $^i$Pr$_2$NEt (0.21 mL, 1.2 mmol). The crude product was purified using flash column chromatography with 95% hexanes/ethyl acetate as the eluent. This procedure afforded 48 mg (40%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.37−7.25 (m, 3 H), 7.16 (d, $J$ = 6.8 Hz, 2 H), 4.80 (d, $J$ = 15.2 Hz, 1 H), 4.09 (d, $J$ = 15.2 Hz, 1 H), 3.63 (s, 3 H), 3.33 (s, 1 H), 1.54 (s, 9 H), 1.34−1.08 (m, 6 H), 1.00−0.91 (m, 2 H), 0.85 (t, $J$ = 7.1 Hz, 3 H), 0.80 (t, $J$ = 7.3 Hz, 3 H), 0.42−0.25 (m, 2 H), 0.25−0.18 (m, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 175.6, 162.1, 135.3, 128.7, 127.9, 127.8, 87.9, 57.4, 50.7, 49.0, 29.7, 28.3, 28.2, 28.0, 27.7, 26.6, 26.5, 14.3, 14.2; IR (neat, ATR) 1723 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + Na]^+$ calcd for $C_{23}H_{38}BNO_4Na$ 426.2792; Found 426.2795.

*4-Benzyl-5-(tert-butyl)-2,2-dibutyl-3-(methoxycarbonyl)-2,3-dihydro-1,4,2-oxazaborol-4-ium-2-uide (**7b**).* General procedure 1 was employed for the transformation of **6b** (103 mg, 0.39 mmol) using 1 M dibutylboron triflate solution in dichloromethane (1.22 mL, 1.25 mmol) and $^i$Pr$_2$NEt (0.26 mL, 1.56 mmol). The crude product was purified using flash column chromatography with 95% hexanes/ethyl acetate as the eluent. This procedure afforded 133 mg (90%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.27 (m, 3 H), 7.15 (d, $J$ = 6.7 Hz, 2 H), 5.20 (d, $J$ = 15.5 Hz, 1 H), 4.42 (d, $J$ = 15.5 Hz, 1 H), 3.59 (s, 3 H), 3.31 (s, 1 H), 1.41 (s, 9 H), 1.35−1.07 (m, 6 H), 1.02−0.94 (m, 2 H), 0.83 (t, $J$ = 7.2 Hz, 6 H), 0.35−0.07 (m, 4 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 183.0, 175.4, 133.9, 129.0, 128.3, 127.5, 51.2, 50.7, 36.2, 28.0, 27.8, 27.7, 26.6, 26.5, 14.3; IR (neat, ATR) 1717 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + Na]^+$ calcd for $C_{23}H_{38}BNO_3Na$ 410.2842; Found 410.2834.

*4-Benzyl-2,2-dibutyl-3-(methoxycarbonyl)-5-methyl-2,3-dihydro-1,4,2-oxazaborol-4-ium-2-uide (**7c**).* General procedure 1 was employed for the transformation of **6c** (44 mg, 0.20 mmol) using 1 M dibutylboron triflate solution in dichloromethane (0.64 mL, 0.64 mmol) and $^i$Pr$_2$NEt (0.14 mL, 0.80 mmol). The crude product was purified using flash column chromatography with 95% hexanes/ethyl acetate as the eluent. This procedure afforded 23 mg (33%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.42−7.30 (m, 3 H), 7.16 (d, $J$ = 6.9 Hz, 2 H), 4.78 (d, $J$ = 15.7 Hz, 1 H), 4.46 (d, $J$ = 15.7 Hz, 1 H), 3.64 (s, 3 H), 3.46 (s, 1 H), 2.28 (s, 3 H), 1.32−1.09 (m, 6 H), 1.00−0.90 (m, 2 H), 0.83 (dt, $J$ = 13.3, 7.2 Hz, 6 H), 0.38−0.30 (m, 2 H), 0.25−0.17 (m, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 175.6, 175.1, 133.7, 129.1, 128.5, 127.5, 51.3, 50.9, 27.9, 27.7, 26.8, 26.5, 16.0, 14.3; IR (neat, ATR) 1719, 1582 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + Na]^+$ calcd for $C_{20}H_{32}BNO_3Na$ 368.2373; Found 368.2359.

*4-Allyl-5-(tert-butoxy)-2,2-dibutyl-3-(methoxycarbonyl)-2,3-dihydro-1,4,2-oxazaborol-4-ium-2-uide (**7d**).* General procedure 1 was employed for the transformation of **6d** (100 mg, 0.44 mmol) using 1 M dibutylboron triflate solution in dichloromethane (1.39 mL, 1.39 mmol) and $^i$Pr$_2$NEt (0.30 mL, 1.74 mmol). The crude product was purified using flash column chromatography with 95% hexanes/ethyl acetate as the eluent. This procedure afforded 134 mg (87%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.76−5.65 (m, 1 H), 5.21−5.15 (m, 2 H), 4.10 (dd, $J$ = 5.0, 15.7 Hz, 1 H), 3.64−3.52 (m, 4 H), 3.47 (s, 1 H), 1.53 (s, 9 H), 1.35−1.03 (m, 8 H), 0.84 (dt, $J$ = 7.2. 12.4 Hz, 6 H), 0.43−0.35 (m, 2 H), 0.23−0.16 (m, 2H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 175.6, 162.0, 131.3, 118.3, 87.6, 76.6, 57.8, 50.7, 47.9, 28.2, 28.0, 27.6, 26.6, 26.5, 14.3, 14.2 (one carbon signal is missing due to incidental overlap); IR (neat, ATR) 1730, 1594 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + Na]^+$ calcd for $C_{19}H_{36}BNO_4Na$ 376.2635; Found 376.2630.

*4-Benzyl-5′-(tert-butyl)-3′-(methoxycarbonyl)-3′H-spiro{bicyclo-[3.3.1]nonane-9,2′-[1,4,2]oxazaborol}-4-ium-9-uide (**7e**).* General procedure 1 was employed for the transformation of **6b** (103 mg, 0.39 mmol) using 0.5 M 9-BBN triflate solution in hexanes (2.50 mL, 1.25 mmol) and $^i$Pr$_2$NEt (0.27 mL, 1.56 mmol), except using a modified workup protocol. The reaction was quenched with 0.5 mL of pH 7 buffer solution, 1.0 mL of methanol, and 0.2 mL of 30% $H_2O_2$. This mixture was allowed to stir for 1 h before 1 mL sodium thiosulfate was added. The biphasic mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted three times with diethyl ether. The crude product was purified using flash column chromatography with 95% hexanes/ethyl acetate as the eluent. This procedure afforded 135 mg (90%) of the title compound as a white solid, mp 171−173 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39−7.38 (m, 3 H), 7.16 (d, $J$ = 7.6 Hz, 2 H), 5.25 (d, $J$ = 15.9 Hz, 1 H), 4.27 (d, $J$ = 16.0 Hz, 1 H), 3.64 (s, 3 H), 3.50 (s, 1 H), 1.95−1.31 (m, 21 H), 0.52 (s, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 183.0, 175.2, 134.2, 129.1, 128.2, 126.9, 51.6, 50.8, 36.2, 32.1, 31.3, 30.9, 30.8, 27.7, 24.6, 24.3; IR (neat, ATR) 1718, 1547 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{23}H_{35}BNO_3$ 384.2710; Found 384.2712.

**Synthesis and Characterization of *N*-Benzyl- and *N*-Allyl-*N*-Aryl Glycine Methyl Esters.** *General Procedure 2.* A flame-dried flask was cooled under a stream of nitrogen and then charged with a solution of aniline (1.0 equiv), aldehyde (1.0 equiv), triethylamine (1.4 equiv), and methanol (0.5 M). This mixture was allowed to stir at rt until the starting material had been completely consumed, as judged by TLC analysis. The solution was then cooled to 0 °C, and $NaBH_4$ (1.0 equiv) was added slowly. The resulting solution was allowed to warm to rt and stirred until the intermediate imine had been completely consumed, as judged by TLC analysis. The reaction mixture was then diluted with water and extracted twice with hexanes. The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5−20% ethyl acetate in hexanes as the eluent.

*General Procedure 3.* A flame-dried flask was cooled under a stream of nitrogen and then charged with a solution of aryl amine (1.0 equiv), methyl bromoacetate (2.0−3.0 equiv), and Hünig's base (3.0 equiv) in acetonitrile (0.1 M). The mixture was heated to reflux with stirring for 24 h and then was cooled to rt and concentrated *in vacuo*. The resulting crude product was partitioned between saturated $NaHCO_3$ and $CH_2Cl_2$. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 3−10% ethyl acetate in hexanes as the eluent.

*N-Benzylaniline.*[27] General procedure 2 was used for the condensation and subsequent reduction of aniline (0.86 mL, 9.42 mmol) and benzaldehyde (0.96 mL, 9.42 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 1.55 g (90%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[27] $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.37


DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

(d, $J$ = 7.5 Hz, 2 H), 7.34 (t, $J$ = 7.3 Hz, 2 H), 7.27 (t, $J$ = 7.4 Hz, 1 H), 7.17 (t, $J$ = 7.6 Hz, 2 H), 6.72 (t, $J$ = 7.3 Hz, 1 H), 6.65 (d, $J$ = 7.8 Hz, 2 H), 4.33 (s, 2 H), 4.12 (s, br, 1 H).

*N-Benzyl-4-bromoaniline.*[28] General procedure 2 was used for the condensation and subsequent reduction of 4-bromoaniline (0.57 mL, 5 mmol) and benzaldehyde (0.51 mL, 5 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 990 mg (76%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[28] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.34 (d, $J$ = 4.5 Hz, 4 H), 7.30−7.22 (m, 3 H), 6.52−6.49 (m, 2 H), 4.30 (s, 2 H), 4.08 (s, br, 1 H).

*N-Benzyl-4-methoxyaniline.*[29] General procedure 2 was used for the condensation and subsequent reduction of 4-anisidine (616 mg, 5 mmol) and benzaldehyde (0.51 mL, 5 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 857 mg (80%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.[29] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.38−7.26 (m, 5 H), 6.80−6.78 (m, 2 H), 6.63−6.59 (m, 2 H), 4.29 (s, 2 H), 3.79 (s, br, 1 H), 3.74 (s, 3 H).

*N-Benzyl-4-(trifluoromethyl)aniline.*[30] General procedure 2 was used for the condensation and subsequent reduction of 4-(trifluoromethyl)-aniline (0.78 mL, 6.20 mmol) and benzaldehyde (0.64 mL, 6.20 mmol). The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 0.734 g (47%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.[30] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.40−7.26 (m, 7 H), 6.63 (d, $J$ = 8.6 Hz, 2 H), 4.38 (s, 3 H).

*N-(4-Bromobenzyl)aniline.*[24] General procedure 2 was used for the condensation and subsequent reduction of aniline (0.46 mL, 5 mmol) and 4-bromobenzaldehyde (0.93 g, 5 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 1.14 g (87%) of the title compound as a pale yellow oil with spectroscopic properties identical to those previously reported.[24] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.47−7.44 (m, 2 H), 7.26−7.23 (m, 2 H), 7.19−7.14 (m, 2 H), 6.72 (t, $J$ = 1.2, 7.4 Hz, 1 H), 6.62−6.59 (m, 2 H), 4.30 (d, $J$ = 4.3 Hz, 2 H), 4.06 (s, br, 1 H).

*N-(2-Bromobenzyl)aniline.*[31] General procedure 2 was used for the condensation and subsequent reduction of aniline (0.46 mL, 5.0 mmol) and 2-bromobenzaldehyde (0.58 mL, 5.0 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 753 mg (57%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[31] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 7.9 Hz, 1 H), 7.40 (d, $J$ = 7.7 Hz, 1 H), 7.27−7.24 (m, 1 H), 7.19−7.11 (m, 3 H), 6.71 (t, $J$ = 7.3 Hz, 1 H), 6.62 (d, $J$ = 7.6 Hz, 2 H), 4.40 (s, 2 H), 4.18 (s, br, 1 H).

*N-(Furan-2-ylmethyl)aniline.*[32] General procedure 2 was used for the condensation and subsequent reduction of aniline (0.95 mL, 10.4 mmol) and furfural (0.86 mL, 10.4 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 1.46 g (81%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[32] $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36 (s, 1 H), 7.18 (dd, $J$ = 6.3, 7.5 Hz, 2 H), 6.74 (t, $J$ = 7.6 Hz, 1 H), 6.68 (d, $J$ = 8.6, 2 H), 6.31 (dd, $J$ = 2.0, 3.2 Hz, 1 H), 6.23 (dd, $J$ = 0.7, 3.1 Hz, 1 H), 4.32 (s, 2 H), 4.04 (s, br, 1 H).

*N-(Thiophen-2-ylmethyl)aniline.*[33] General procedure 2 was used for the condensation and subsequent reduction of aniline (0.46 mL, 5.0 mmol) and thiophene-2-carboxaldehyde (0.47 mL, 5.0 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 190 mg (20%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[33] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.22−7.17 (m, 3 H), 7.02−7.00 (m, 1 H), 6.97 (dd, $J$ = 5.1 Hz, 1 H), 6.74 (tt, $J$ = 7.4, 1.1 Hz, 1 H), 6.69−6.67 (m, 2 H), 4.51 (d, $J$ = 1.0 Hz, 2 H), 4.05 (s, br, 1 H).

*N-[(1-Tosyl-1H-pyrrol-2-yl)methyl]aniline.*[34] A slightly modified general procedure 2 was used for the condensation (16 h, 60 °C) and subsequent reduction of aniline (0.11 mL, 1.22 mmol) and 1-tosyl-1*H*-pyrrole-2-carbaldehyde (304 mg, 1.22 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 68.4 mg (17%) of the title compound as a white solid, mp 78−82 °C, with spectroscopic properties identical to those previously reported.[34] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.64 (d, $J$ = 8.4 Hz, 2 H), 7.30−7.24 (m, 3 H), 7.10 (dd, $J$ = 8.4, 7.6 Hz, 2 H), 6.68 (t, $J$ = 7.2 Hz, 1 H), 6.45 (d, $J$ = 7.9 Hz, 2 H), 7.20−7.18 (m, 2 H), 4.38 (d, $J$ = 5.0 Hz, 2 H), 4.05 (s, br, 1 H), 2.40 (s, 3 H).

*N-Crotylaniline.*[35] General procedure 2 was used for the condensation of crotonaldehyde (0.41 mL, 5.0 mmol) with aniline (0.46 mg, 5.0 mmol) and $NEt_3$ (0.7 mL, 5.0 mmol) in 10 mL of methanol. The subsequent reduction was carried out with $NaBH_4$ (265 mg, 7.0 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 406 mg (55%) of 4-methylpent-2-yn-1-ol as a colorless oil with spectroscopic properties identical to those previously reported.[35] $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.15−7.19 (m, 2 H), 6.68−6.71 (m, 1 H), 6.60−6.63 (m, 2 H), 5.68−5.74 (m, 1 H), 5.57−5.62 (m, 1 H), 3.68−3.69 (m, 3 H), 1.70 (dd, $J$ = 1.5, 6.4 Hz, 3 H).

*N-Cinnamylaniline.*[36] General procedure 2 was used for the condensation of cinnamaldehyde (1 g, 14.7 mmol) with aniline (620 mg, 20.6 mmol) and $NEt_3$ (11.0 mL, 17.6 mmol) in 18 mL of methanol. The subsequent reduction was carried out with $LiAlH_4$ (1.47 mL, 5 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 1.2 g (55%) of 4-methylpent-2-yn-1-ol as a pale yellow oil with spectroscopic properties identical to those previously reported.[36] $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38−7.29 (m, 4 H), 7.24−7.17 (m, 3 H), 6.74−6.61 (m, 4 H), 6.37−6.30 (m, 1 H), 3.94 (d, $J$ = 5.6 Hz, 2 H), 3.84 (s, br, 1 H).

*N-(2-Methylallyl)aniline.*[37] A flame-dried flask was cooled under a stream of nitrogen and charged with a solution of 3-chloro-2-methyl-propene (0.69 mL, 7 mmol) in acetonitrile (28 mL, 0.25 M). To this solution was added aniline (1.28 mL, 14 mmol) and $NEt_3$ (1.95 mL, 14 mmol). This solution was heated to reflux overnight and then was cooled to rt. The solvent was removed *in vacuo*, and the crude product was purified by flash column chromatography on silica gel with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 394 mg (38%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[37] $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.13−7.18 (m, 2 H), 6.68 (td, $J$ = 1.0, 7.4 Hz, 1 H), 6.59 (dd, $J$ = 1.0, 8.5 Hz, 2 H), 4.96 (s, 1 H), 4.87 (s, 1 H), 3.67 (s, 2 H), 1.78 (s, 3 H).

*N-(3-Methylbut-2-en-1-yl)aniline.*[38] General procedure 2 was used for the condensation of 3-methyl-2-butenal (0.48 mL, 5 mmol) with aniline (0.46 mL, 5 mmol) and $NEt_3$ (0.7 mL, 5 mmol) in 10 mL of methanol. The subsequent reduction was carried out with $NaBH_4$ (265 mg, 7 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 656 mg (81%) of the title compound as a yellow oil with spectroscopic properties identical to those previously reported.[38] $^1$H NMR (400 MHz, Chloroform-*d*) d 7.23−7.13 (m, 2 H), 6.71 (t, $J$ = 7.3 Hz, 1 H), 6.66−6.58 (m, 2 H), 5.34 (t, $J$ = 6.7 Hz, 1 H), 3.69 (d, $J$ = 6.7 Hz, 2 H), 3.57 (s, br, 1 H), 1.74 (d, $J$ = 14.7 Hz, 6 H).

*(E)-4-Methoxy-N-(oct-2-en-1-yl)aniline.* General procedure 2 was used for the condensation of 2-octenal (0.75 mL, 5 mmol) with *p*-anisidine (616 mg, 5 mmol) and $NEt_3$ (0.7 mL, 5 mmol) in 10 mL of methanol. The subsequent reduction was carried out with $NaBH_4$ (265 mg, 7 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 711 mg (61%) of the title compound as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.79 (d, $J$ = 8.8 Hz, 2 H), 6.60 (d, $J$ = 8.9 Hz, 2 H), 5.69 (dt, $J$ = 15.1, 6.6 Hz, 1 H), 5.57 (dt, $J$ = 15.4, 5.5 Hz, 1 H), 3.75 (s, 3 H), 3.65 (d, $J$ = 6.1 Hz, 2 H), 3.42 (s, br, 1 H), 2.02 (q, $J$ = 7.4 Hz, 2 H), 1.44−1.21 (m, 6 H), 0.89 (t, $J$ = 7.1 Hz, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 152.1, 142.5, 133.4, 127.0,



DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

114.8, 114.3, 55.8, 47.1, 32.3, 31.4, 28.9, 22.5, 14.0; IR (neat, ATR) 3394, 1511, 1233 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{15}H_{24}NO$ 234.1858; Found 234.1850.

*(E)-4-Chloro-N-(pent-2-en-1-yl)aniline.* General procedure 2 was used for the condensation of 2-pentenal (0.49 mL, 5 mmol) with 4-chloroaniline (638 mg, 5 mmol) and $NEt_3$ (0.7 mL, 5 mmol) in 10 mL of methanol. The subsequent reduction was carried out with $NaBH_4$ (265 mg, 7 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 505 mg (52%) of the title compound as a colorless oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.09 (d, $J$ = 8.0 Hz, 2 H), 6.51 (d, $J$ = 8.2 Hz, 2 H), 5.74 (ddt, $J$ = 15.3, 6.3, 1.2 Hz, 1 H), 5.53 (dt, $J$ = 15.3, 5.5 Hz, 1 H), 3.72−3.61 (m, 3 H), 2.08−2.01 (m, 2 H), 0.98 (td, $J$ = 1.0, 7.5 Hz, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 146.8, 135.2, 129.0, 125.3, 121.8, 114.0, 46.1, 25.3, 13.5; IR (neat, ATR) 3415, 1600 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{15}ClN$ 196.0893; Found 196.0885.

*N-(Cyclohex-1-en-1-ylmethyl)aniline.*[39] General procedure 2 was used for the condensation of 1-cyclohexene-1-carboxaldehyde (0.52 mL, 4.54 mmol) with aniline (0.42 mL, 4.54 mmol) and $NEt_3$ (0.63 mL, 4.54 mmol) in 9 mL of methanol. The subsequent reduction was carried out with $NaBH_4$ (240 mg, 6.36 mmol). The crude product was purified using flash column chromatography with 80% hexanes/ethyl acetate as the eluent. This procedure afforded 682 mg (80%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[39] $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.15 (dd, $J$ = 8.6, 7.2 Hz, 2 H), 6.67 (t, $J$ = 7.3 Hz, 1 H), 6.67−6.56 (m, 2 H), 5.66 (s, 1 H), 3.74 (s, 1 H), 3.59 (s, 2 H), 2.06−1.95 (m, 5 H), 1.69−1.51 (m, 3 H).

*Methyl 2-[Benzyl(Phenyl)amino]acetate (**9a**).* General procedure 3 was used for the alkylation of *N*-benzylaniline (712 mg, 3.9 mmol) with bromoacetic acid (0.74 mL, 7.8 mmol) and $^iPr_2NEt$ (2.0 mL, 11.7 mmol) in 39 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 539 mg (54%) of the title compound as a pale yellow solid, mp 52−55 °C, with spectroscopic properties identical to those previously reported.[40] $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.24 (m, 5 H), 7.22−7.19 (m, 2 H), 6.77 (t, $J$ = 7.4 Hz, 1 H), 6.70 (d, $J$ = 7.8 Hz, 2 H), 4.65 (s, 2 H), 4.10 (s, 2 H), 3.74 (s, 3 H). $^{13}C$ NMR (176 MHz, $CDCl_3$) $\delta$ 171.6, 148.4, 138.2, 129.3, 128.7, 127.1, 126.8, 117.9, 112.7, 55.7, 52.3, 52.0.

*Methyl 2-[Benzyl(4-bromophenyl)amino]acetate (**9b**).* General procedure 3 was used for the alkylation of *N*-benzyl-4-bromoaniline (350 mg, 1.33 mmol) with bromoacetic acid (0.38 mL, 3.99 mmol) and $^iPr_2NEt$ (0.70 mL, 3.99 mmol) in 13 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 289 mg (65%) of the title compound as a pale yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.22 (t, $J$ = 7.0 Hz, 2 H), 7.28−7.24 (m, 5 H), 6.56−6.53 (m, 2 H), 4.61 (s, 2 H), 4.07 (s, 2 H), 3.74 (s, 3 H); $^{13}C$ NMR (176 MHz, $CDCl_3$) $\delta$ 171.2, 147.5, 137.7, 131.9, 128.8, 127.3, 126.7, 114.2, 109.7, 55.7, 52.4, 52.1; IR (neat, ATR) 1745 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0436.

*Methyl 2-[Benzyl(4-methoxyphenyl)amino]acetate (**9c**).* General procedure 3 was used for the alkylation of *N*-benzy-4-methoxylaniline (540 mg, 2.53 mmol) with bromoacetic acid (0.72 mL, 7.59 mmol) and $^iPr_2NEt$ (1.32 mL, 7.59 mmol) in 25 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 487 mg (67%) of the title compound as a yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.25 (m, 5 H), 6.80−6.78 (m, 2 H), 6.69−6.66 (m, 2 H), 4.59 (s, 2 H), 4.04 (s, 2 H), 3.74 (s, 3 H), 3.72 (s, 3 H); $^{13}C$ NMR (176 MHz, $CDCl_3$) $\delta$ 171.4, 152.2, 143.1, 138.7, 128.6, 127.1, 127.0, 114.8, 114.4, 56.2, 55.7, 52.8, 51.9; IR (neat, ATR) 1741 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$ 286.1443; Found 286.1439.

*Methyl 2-{Benzyl[4-(trifluoromethyl)phenyl]amino}acetate (**9d**).* General procedure 3 was used for the alkylation of *N*-benzyl-4-(trifluoromethyl)aniline (130 mg, 0.517 mmol) with bromoacetic acid (0.1 mL, 1.03 mmol) and $^iPr_2NEt$ (0.27 mL, 1.55 mmol) in 5 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 37 mg (22%) of the title compound as a yellow oil. $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.43 (d, $J$ = 8.6 Hz, 2 H), 7.34 (t, $J$ = 7.1 Hz, 2 H), 7.29−7.24 (m, 3 H), 6.69 (d, $J$ = 8.6 Hz, 2 H), 4.69 (s, 2 H), 4.14 (s, 2 H), 3.76 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 170.8, 150.8, 137.2, 128.9, 127.4, 126.64, 126.61, 126.59, 126.55, 111.7, 55.6, 52.2, 52,1; IR (neat, ATR) 1746 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{17}F_3NO_2$ 324.1211; Found 324.1204.

*Methyl 2-[(4-Bromobenzyl)(phenyl)amino]acetate (**9e**).* General procedure 3 was used for the alkylation of *N*-(4-bromobenzyl)aniline (459 mg, 1.75 mmol) with bromoacetic acid (0.50 mL, 5.25 mmol) and $^iPr_2NEt$ (0.91 mL, 5.25 mmol) in 18 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 368 mg (63%) of the title compound as a yellow solid, mp 97−100 °C. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.46−7.43 (m, 2 H), 7.22−7.17 (m, 4 H), 6.80 (t, $J$ = 7.3 Hz, 1 H), 6.65 (d, $J$ = 8.1 Hz, 2 H), 4.59 (s, 2 H), 4.08 (s, 2 H), 3.74 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 171.5, 148.2, 137.5, 131.8, 129.3, 128.5, 120.8, 118.0, 112.6, 55.3, 52.4, 52.0; IR (neat, ATR) 1746 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0437.

*Methyl 2-[(2-Bromobenzyl)(phenyl)amino]acetate (**9f**).* General procedure 3 was used for the alkylation of *N*-(2-bromobenzyl)aniline (700 mg, 2.67 mmol) with bromoacetic acid (0.76 mL, 8.01 mmol) and $^iPr_2NEt$ (1.40 mL, 8.01 mmol) in 27 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 256 mg (40%) of the title compound as a pale yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.59−7.58 (m, 1 H), 7.29−7.18 (m, 4 H), 7.15−7.12 (m, 1 H), 6.77 (t, $J$ = 7.4 Hz, 1 H), 6.59 (d, $J$ = 8.1 Hz, 2 H), 4.65 (s, 2 H), 4.14 (s, 2 H), 3.78 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 171.5, 147.9, 136.8, 132.9, 129.3, 128.6, 128.1, 127.6, 122.7, 117.8, 112.3, 56.7, 52.8, 52.1; IR (neat, ATR) 1748 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0435.

*Methyl 2-[(Furan-2-ylmethyl)(phenyl)amino]acetate (**9g**).* General procedure 3 was used for the alkylation of *N*-(furan-2-ylmethyl)aniline (455 mg, 2.63 mmol) with bromoacetic acid (0.37 mL, 3.94 mmol) and $^iPr_2NEt$ (1.37 mL, 7.88 mmol) in 26 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 534 mg (83%) of the title compound as a pale yellow oil. $^1H$ NMR (700 MHz, $CDCl_3$) $\delta$ 7.37 (s, 1 H), 7.22 (t, $J$ = 7.9 Hz, 2 H), 6.79−6.76 (m, 3 H), 6.31 (d, $J$ = 3.0 Hz, 1 H), 6.24 (d, $J$ = 3.0 Hz, 1 H), 4.55 (d, 2 H), 4.07 (s, 2 H), 3.73 (s, 3 H); $^{13}C$ NMR (176 MHz, $CDCl_3$) $\delta$ 171.6, 151.8, 148.1, 142.2, 129.2, 118.0, 112.9, 110.3, 107.8, 52.0, 51.8, 48.5; IR (neat, ATR) 1735 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{16}NO_3$ 246.1130; Found 246.1129.

*Methyl N-Phenyl-N-(thiophen-2-ylmethyl)glycinate (**9h**).* General procedure 3 was used for the alkylation of *N*-(thiophene-2-ylmethyl)-aniline (156 mg, 0.82 mmol) with bromoacetic acid (0.12 mL, 1.23 mmol) and $^iPr_2NEt$ (0.43 mL, 2.46 mmol) in 8.2 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 160.6 mg (75%) of the title compound as a colorless oil. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.28−7.19 (m, 3 H), 7.00−6.93 (m, 2 H), 6.83−6.73 (m, 3 H), 4.78 (s, 2 H), 4.09 (s, 2 H), 3.74 (s, 3 H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$ 171.5, 148.1, 142.0, 129.3, 126.9, 125.2, 124.7, 118.2, 113.1, 52.0, 51.6, 50.9; IR (neat, ATR) 1740, 1504 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{16}NO_2S$ 262.0902; Found 262.0893.

*Methyl N-Phenyl-N-[(1-tosyl-1H-pyrrol-2-yl)methyl]glycinate (**9i**).* General procedure 3 was used for the alkylation of *N*-(thiophene-2-ylmethyl)aniline (150 mg, 046 mmol) with bromoacetic acid (0.07 mL, 0.69 mmol) and $^iPr_2NEt$ (0.24 mL, 1.38 mmol) in 4.6 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 119.2 mg (65%) of the title compound as a pale yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.66 (d, $J$ = 8.2 Hz, 2 H), 7.38 (dd, $J$ = 3.3, 1.8 Hz,



DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

1 H), 7.29 (d, $J$ = 8.1 Hz, 2 H), 7.13−7.05 (m, 2 H), 6.72 (t, $J$ = 7.1 Hz, 1 H), 6.37 (d, $J$ = 8.1 Hz, 2 H), 6.21 (t, $J$ = 3.3 Hz, 1 H), 6.14−6.09 (m, 1 H), 4.67 (s, 2 H), 3.81 (s, 2 H), 3.71 (s, 3 H), 2.44 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 171.4, 147.6, 145.0, 136.1, 130.8, 130.0, 129.1, 126.9, 123.4, 117.9, 114.2, 112.5, 111.5, 52.0, 51.6, 49.1, 21.6; IR (neat, ATR) 1749, 1505, 1365 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + Na]^+$ calcd for $C_{21}H_{22}N_2O_4SNa$ 421.1198; Found 421.1197.

*Methyl-2-[allyl(phenyl)amino]acetate (**14a**).*[41] General procedure 3 was used for the alkylation of *N*-allylaniline (418 mg, 3.14 mmol) with methylbromoacetate (0.60 mL, 6.28 mmol) and $^i$Pr$_2$NEt (1.64 mL, 9.42 mmol) in 31 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 546 mg (85%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[41] $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.21 (td, $J$ = 1.8, 7.3 Hz, 2 H), 6.75 (t, $J$ = 7.3 Hz, 1 H), 6.66 (d, $J$ = 8.1 Hz, 2 H), 5.89 (ddt, $J$ = 17.2, 10.1, 5.0 Hz, 1 H), 5.18−5.25 (m, 2 H), 4.04 (s, 2 H), 4.03 (d, $J$ = 4.9 Hz, 2 H), 3.74 (s, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 171.8, 148.1, 133.7, 129.2, 117.5, 116.6, 112.4, 54.2, 52.0, 51.9.

*Methyl-2-[crotyl(phenyl)amino]acetate (**14b**).* General procedure 3 was used for the alkylation of *N*-crotylaniline (353 mg, 2.40 mmol) with methylbromoacetate (0.34 mL, 3.6 mmol) and $^i$Pr$_2$NEt (1.25 mL, 7.2 mmol) in 24 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 389 mg (74%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.21 (t, $J$ = 7.3 Hz, 2 H), 6.73 (t, $J$ = 7.2 Hz, 1 H), 6.70 (t, $J$ = 8.0 Hz, 2 H), 5.65 (dq, $J$ = 15.3, 6.5 Hz, 1 H), 5.51 (dt, $J$ = 15.3, 5.6 Hz 1 H), 4.01 (s, 2 H), 3.94 (d, $J$ = 5.6 Hz, 2 H), 3.72 (s, 3 H), 1.70 (d, $J$ = 6.3 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 171.9, 148.3, 129.2, 128.1, 126.4, 117.3, 112.5, 53.3, 52.0, 51.6, 17.7; IR (neat, ATR) 1746 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$ 220.1338; Found 220.1332.

*Methyl-2-[cinnamyl(phenyl)amino]acetate (**14c**).* General procedure 3 was used for the alkylation of *N*-cinnamylaniline (168 mg, 0.805 mmol) with methylbromoacetate (0.11 mL, 1.2 mmol) and $^i$Pr$_2$NEt (0.42 mL, 2.4 mmol) in 8 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 148 mg (65%) of the title compound as a pale yellow solid, mp 46−49 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35−7.37 (m, 2 H), 7.25−7.32 (m, 2 H), 7.21−7.25 (m, 3 H), 6.77 (t, $J$ = 7.3 Hz, 1 H), 6.72 (dd, $J$ = 1.0, 9.0 Hz, 2 H), 6.56 (d, $J$ = 15.9 Hz, 1 H), 6.28 (dt, $J$ = 5.3, 15.8 Hz, 1 H), 4.19 (dd, $J$ = 1.4, 5.3 Hz, 2 H), 4.09 (s, 2 H), 3.74 (s, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 171.8, 148.3, 136.7, 131.6, 129.3, 128.6, 127.5, 126.4, 125.5, 117.6, 112.5, 53.8, 52.0, 51.9; IR (neat, ATR) 1747 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{20}NO_2$ 282.1494; Found 282.1492.

*Methyl-2-[(3-methylbut-2-en-1-yl)(phenyl)amino]acetate (**14d**).* General procedure 3 was used for the alkylation of *N*-(3-methylbut-2-en-1-yl)aniline (666 mg, 4.13 mmol) with methylbromoacetate (0.59 mL, 6.19 mmol) and $^i$Pr$_2$NEt (2.16 mL, 12.38 mmol) in 41 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 869 mg (90%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.24−7.15 (m, 2 H), 6.76−6.62 (m, 3 H), 5.31−5.20 (m, 1 H), 4.03−3.93 (m, 4 H), 3.71 (s, 3 H), 1.71 (d, $J$ = 14.5 Hz, 6 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 172.0, 148.5, 135.6, 129.2, 120.9, 117.3, 112.6, 51.9, 51.7, 49.1, 25.8, 17.9; IR (neat, ATR) 1745, 1598 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$ 234.1494; Found 234.1484.

*Methyl-2-[(2-methylallyl)(phenyl)amino])acetate (**14e**).* General procedure 3 was used for the alkylation of *N*-(2-methylallyl)aniline (394 mg, 2.67 mmol) with methylbromoacetate (0.38 mL, 4.05 mmol) and $^i$Pr$_2$NEt (1.40 mL, 8.1 mmol) in 27 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 437 mg (75%) of 4-methylpent-2-yn-1-ol as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.19 (t, $J$ = 7.4 Hz, 2 H), 6.71 (t, $J$ = 7.3 Hz, 1 H), 6.61 (d, $J$ = 8.3 Hz, 2 H), 4.86 (s, 2 H), 4.02 (s, 2 H), 3.88 (s, 2 H), 3.72 (s, 3 H), 1.73 (s, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 171.8, 148.5, 140.9, 129.1, 117.3, 112.2, 111.1, 57.7, 51.91, 51.89, 19.9; IR (neat, ATR) 1746 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$ 220.1338; Found 220.1331.

*(E)-Methyl 2-[(4-Methoxyphenyl)(oct-2-en-1-yl)amino]acetate (**14f**).* General procedure 3 was used for the alkylation of (*E*)-4-methoxy-*N*-(oct-2-en-1-yl)aniline (710 mg, 3.04 mmol) with methylbromoacetate (0.43 mL, 4.56 mmol) and $^i$Pr$_2$NEt (1.59 mL, 9.12 mmol) in 30 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 554 mg (89%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.79 (d, $J$ = 9.2 Hz, 2 H), 6.65 (d, $J$ = 9.0 Hz, 2 H), 5.63 (dt, $J$ = 15.3, 6.7 Hz, 1 H), 5.48 (dt, $J$ = 15.4, 5.7 Hz, 1 H), 3.95 (s, 2 H), 3.87 (d, $J$ = 5.9 Hz, 2 H), 3.72 (s, 3 H), 3.69 (s, 3 H), 2.06−1.96 (m, 2 H), 1.40−1.16 (m, 6 H), 0.86 (t, $J$ = 6.9 Hz, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 172.1, 152.1, 143.2, 133.9, 125.5, 114.7, 114.6, 55.7, 54.0, 52.2, 51.8, 32.2, 31.3, 28.9, 22.5, 14.0; IR (neat, ATR) 1745, 1512 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{28}NO_3$ 306.2069; Found 306.2069.

*(E)-Methyl 2-[(4-Chlorophenyl)(pent-2-en-1-yl)amino]acetate (**14g**).* General procedure 3 was used for the alkylation of (*E*)-4-chloro-*N*-(pent-2-en-1-yl)aniline (505 mg, 2.58 mmol) with methylbromoacetate (0.37 mL, 3.87 mmol) and $^i$Pr$_2$NEt (1.35 mL, 7.74 mmol) in 26 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 479 mg (69%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.17−7.08 (m, 2 H), 6.61−6.50 (m, 2 H), 5.65 (dt, $J$ = 6.3, 15.5 Hz, 1 H), 5.45 (dt, $J$ = 15.4, 5.6 Hz, 1 H), 3.98 (s, 2 H), 3.90 (d, $J$ = 5.7 Hz, 2 H), 3.71 (s, 3 H), 2.09−2.02 (m, 2 H), 0.96 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 171.5, 147.0, 135.4, 128.9, 123.7, 122.1, 113.6, 53.5, 52.0, 51.7, 25.2, 13.5; IR (neat, ATR) 1745, 1598, 1498 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{19}ClNO_2$ 268.1104; Found 268.1099.

*Methyl 2-[(Cyclohex-1-en-1-ylmethyl)(phenyl)amino]acetate (**14h**).* General procedure 3 was used for the alkylation of *N*-(cyclohex-1-en-1-ylmethyl)aniline (0.5 mg, 2.67 mmol) with methylbromoacetate (0.38 mL, 4.01 mmol) and $^i$Pr$_2$NEt (1.40 mL, 8.01 mmol) in 27 mL of $CH_3CN$. The crude product was purified using flash column chromatography with 90% hexanes/ethyl acetate as the eluent. This procedure afforded 554 mg (78%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.19 (t, $J$ = 8.1 Hz, 2 H), 6.71 (t, $J$ = 7.3 Hz, 1 H), 6.64 (d, $J$ = 8.1 Hz, 2 H), 5.57 (s, 1 H), 4.00 (s, 2 H), 3.84 (s, 2 H), 3.72 (s, 3 H), 2.00 (s, 2 H), 1.91 (s, 2 H), 1.65−1.62 (m, 2 H), 1.62−1.53 (m, 2 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 171.9, 148.8, 133.3, 129.1, 122.9, 117.1, 112.3, 57.6, 51.9, 51.5, 26.3, 25.0, 22.6, 22.5; IR (neat, ATR) 1748 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$ 260.1651; Found 260.1653.

*2-[Phenyl(1-phenylethyl)amino]acetic Acid.* A flame-dried flask was cooled under a stream of nitrogen and charged with *N*-phenylglycine (200 mg, 1.32 mmol) and THF (2.7 mL), and the resulting solution was cooled to −78 °C. To this solution was added *n*-BuLi (1.16 mL, 2.5 M solution in hexanes). After stirring for 15 min, 1-(bromoethyl)-benzene (0.2 mL, 1.46 mmol) was added dropwise, and the mixture was allowed to warm to rt over 2 h. The reaction was then quenched with saturated sodium bicarbonate solution, and the resulting mixture was transferred to a separatory funnel. The layers were separated, and the aqueous layer was washed twice with ethyl acetate. The aqueous layer was then acidified with $H_2SO_4$ and then extracted three times with diethyl ether. The combined ether layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with 60% hexanes/ethyl acetate as the eluent to afford 167 mg (49%) of the title compound as a white solid, mp 108−114 °C. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 10.68 (s, br, 1 H), 7.37−7.30 (m, 4 H), 7.25−7.22 (m, 3 H), 6.79 (t, $J$ = 7.3 Hz, 1 H), 6.75 (d, $J$ = 8.3 Hz, 2 H), 5.18 (q, $J$ = 6.9 Hz, 1 H), 3.95 (s, 2 H), 1.62 (d, $J$ = 6.9 Hz, 3 H); $^{13}$C NMR (176 MHz,



DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

$CDCl_3$) $\delta$ 176.9, 148.1, 141.9, 129.4, 128.7, 127.3, 127.0, 118.6, 113.9, 57.0, 48.5, 17.9; IR (neat, ATR) 1720 $cm^{-1}$. HRMS (ESI−, magnetic sector) $m/z$: $[M - H]^-$ calcd for $C_{16}H_{16}NO_2$ 254.1181; Found 254.1187.

*Methyl 2-[Phenyl(1-phenylethyl)amino]acetate (**11**).* A flame-dried flask was cooled under a stream of nitrogen and charged with methanol (16 $\mu$L, 0.407 mmol) and dichloromethane (2.0 mL, 0.2 M), and the resulting solution was cooled to 0 °C. DMAP (25 mg, 0.204 mmol), EDC (78 mg, 0.407 mmol), and 2-[phenyl(1-phenylethyl)amino]acetic acid (104 mg, 0.407 mmol) were added, and the mixture was allowed to warm to rt overnight. The dichloromethane was removed *in vacuo*, and the resulting crude oil was diluted with water and ethyl acetate. The mixture was transferred to a separatory funnel, the layers were separated, and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with 90% hexanes/ethyl acetate as the eluent to afford 84 mg (76%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.35−7.28 (m, 4 H), 7.27−7.17 (m, 3 H), 6.77−6.68 (m, 3 H), 5.17 (q, $J$ = 7.0 Hz, 1 H), 3.95 (s, 2 H), 3.69 (s, 3 H), 1.60 (d, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 172.2, 148.5, 142.4, 129.3, 128.6, 127.1, 127.0, 117.7, 113.2, 56.5, 52.0, 48.5, 18.1; IR (neat, ATR) 1750, 1597 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1494; Found 270.1496.

*Methyl 2-[Benzyl(phenyl)amino]propanoate (**13**).* A flame-dried flask was cooled under a stream of nitrogen and then charged with $^i$Pr$_2$NH (0.11 mL, 0.76 mmol) in THF (0.5 mL). The reaction mixture was cooled to −78 °C. Then, a 1.6 M solution of *n*-BuLi in hexanes (0.4 mL, 0.65 mmol) was added, and the resulting solution was stirred for 5 min. To this solution was added compound **9a** (150 mg, 0.59 mmol) in THF (0.5 mL). After stirring for 15 min, iodomethane (0.44 mL, 0.71 mmol) was added, and the resulting solution was stirred for 15 min at −78 °C and then 1 h at 0 °C. The mixture was warmed to rt, diluted with $NH_4Cl$ and EtOAc, and transferred to a separatory funnel. The layers were separated, and the organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with 90% hexanes/ethyl acetate as the eluent to afford 78 mg (49%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31 (d, $J$ = 4.4 Hz, 4 H), 7.23−7.19 (m, 1 H), 7.19−7.15 (m, 2 H), 6.74 (t, $J$ = 7.4 Hz, 1 H), 6.70 (d, $J$ = 8.1 Hz, 2 H), 4.70−7.53 (m, 3 H), 3.70 (s, 3 H), 1.50 (d, $J$ = 7.4, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 174.3, 148.9, 140.1, 129.1, 128.5, 126.6, 126.3, 117.9, 113.7, 56.7, 52.1, 52.0, 16.2; IR (neat, ATR) 1733 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1494; Found 270.1491.

*Methyl N-Allyl-N-phenylalaninate (**17**).* A flame-dried flask was cooled under a stream of nitrogen and then charged with $^i$Pr$_2$NH (0.09 mL, 0.63 mmol) in THF (0.4 mL). After cooling to −78 °C, a 2.5 M solution of *n*-BuLi in hexanes (0.21 mL, 0.54 mmol) was added, and the resulting solution was stirred for 5 min. To this solution was added compound **14a** (100 mg, 0.49 mmol) in THF (0.4 mL). After stirring for 15 min, iodomethane (0.036 mL, 0.58 mmol) was added, and the resulting solution was stirred for 15 min at −78 °C and then 1 h at 0 °C. The mixture was warmed to rt and diluted with $NH_4Cl$ and EtOAc. The layers were separated, and the organic layers were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with 80% hexanes/ethyl acetate as the eluent to afford 65 mg (61%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.27−7.17 (m, 2 H), 6.78−6.70 (m, 3 H), 5.92 (ddt, $J$ = 17.2, 10.3, 4.4 Hz, 1 H), 5.28−5.23 (m, 1 H), 5.18−5.14 (m, 1 H), 4.48 (q, $J$ = 7.2 Hz, 1 H), 4.07−4.02 (m, 1 H), 3.96−3.90 (m, 1 H), 3.70 (d, $J$ = 3.8 Hz, 3 H), 1.50 (d, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 174.3, 148.7, 136.1, 129.1, 117.6, 115.6, 113.5, 56.3, 52.0, 50.5, 16.0; IR (neat, ATR) 1734 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$ 220.1338; Found 220.1333.

*(1S,2R)-2-Phenylcyclohexyl 2-[Benzyl(phenyl)amino]acetate (**21a**).* A flame-dried flask was cooled under a stream of nitrogen and charged with *trans*-2-phenylcyclohexanol (140 mg, 0.792 mmol) and dichloromethane (4 mL, 0.2 M), and the resulting solution was cooled to 0 °C. DMAP (48 mg, 0.396 mmol), EDC (151 mg, 0.792 mmol), and 2-(benzyl(phenyl)amino)acetic acid (191 mg, 0.792 mmol), which was prepared according to a published procedure,[42] were added, and the mixture was allowed to warm to rt overnight. The dichloromethane was removed *in vacuo*, and the crude oil was diluted with water and ethyl acetate. The mixture was transferred to a separatory funnel, the layers were separated, and the organic layer was dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with 90% hexanes/ethyl acetate as the eluent to afford 214 mg (68%) of the title compound as a white solid, mp 110−112 °C. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.31−7.16 (m, 8 H), 7.12 (d, $J$ = 7.4 Hz, 2 H), 7.09−7.04 (m, 2 H), 6.68 (t, $J$ = 7.3 Hz, 1 H), 6.33 (d, $J$ = 7.8 Hz, 2 H), 5.07 (td, $J$ = 10.8, 4.4 Hz, 1 H), 4.38 (d, $J$ = 17.1 Hz, 1 H), 4.28 (d, $J$ = 17.1 Hz, 1 H), 3.74 (d, $J$ = 4.3 Hz, 2 H), 2.68−2.61 (m, 1 H), 2.12−2.07 (m, 1 H), 1.93 (d, $J$ = 13.4 Hz, 1 H), 1.86−1.84 (m, 1 H), 1.79−1.74 (m, 1 H), 1.59−1.31 (m, 4 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 170.3, 148.6, 142.9, 138.5, 129.0, 128.5, 128.4, 127.6, 126.9, 126.7, 126.5, 117.3, 112.3, 76.6, 55.3, 52.0, 50.0, 33.8, 32.2, 25.7, 24.7; IR (neat, ATR) 1744 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{27}H_{30}NO_2$ 400.2277; Found 400.2269.

*2-[Allyl(phenyl)amino]acetic Acid.* A flame-dried flask was cooled under a stream of nitrogen and charged with *N*-phenylglycine (302 mg, 2 mmol) and THF (4.0 mL, 0.5 M), and the resulting solution was cooled to −78 °C. To this solution was added *n*-BuLi (1.76 mL, 2.5 M solution in hexanes). After stirring for 15 min, allyl bromide (0.26 mL, 2.2 mmol) was added dropwise, and the mixture was allowed to warm to rt over 2 h. The reaction was then quenched with 1 M HCl, and the resulting mixture was extracted three times with ethyl acetate. The combined ether layers were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with 60% hexanes/ethyl acetate as the eluent to afford 349 mg (91%) of the title compound as a brown oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.26−7.19 (m, 2 H), 6.78 (t, $J$ = 7.3 Hz, 1 H), 6.69 (d, $J$ = 7.9 Hz, 2 H), 5.91−5.88 (m, 1 H), 5.26−5.21 (m, 2 H), 4.05 (s, 2 H), 4.00 (d, $J$ = 5.3 Hz, 2 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 177.4, 148.0, 133.5, 129.3, 117.9, 117.0, 112.6, 54.2, 51.8; IR (neat, ATR) 2920, 1722 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{11}H_{14}NO_2$ 192.1025; Found 192.1017.

*(1S,2R)-2-Phenylcyclohexyl-2-[allyl(phenyl-$\lambda^4$azanyl)]acetate (**21b**).* A flame-dried flask was cooled under a stream of nitrogen and charged with *trans*-2-phenylcyclohexanol (322 mg, 1.83 mmol) and dichloromethane (9.1 mL, 0.2 M), and the resulting solution was cooled to 0 °C. DMAP (112 mg, 0.92 mmol), EDC (349 mg, 1.83 mmol), and 2-[allyl(phenyl)amino]acetic acid (349 mg, 1.83 mmol) were added, and the mixture was allowed to warm to rt overnight. The dichloromethane was removed *in vacuo*, and the crude oil was diluted with water and ethyl acetate. The mixture was transferred to a separatory funnel, the layers were separated, and the organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel with 90% hexanes/ethyl acetate as the eluent to afford 310 mg (49%) of the title compound as a white solid, mp 101−104 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.33−7.16 (m, 5 H), 7.12−7.05 (m, 2 H), 6.72 (t, $J$ = 7.1 Hz, 1 H), 6.36 (d, $J$ = 8.0 Hz, 2 H), 5.72 (ddt, $J$ = 16.9, 10.3, 5.0 Hz, 1 H), 5.14−5.09 (m, 3 H), 3.82−3.68 (m, 4 H), 2.72−2.68 (m, 1 H), 2.17−2.15 (m, 1 H), 1.99−1.96 (m, 1 H), 1.91−1.88 (m, 1 H), 1.82−1.80 (m, 1 H), 1.63−1.37 (m, 4 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 170.4, 148.3, 143.0, 133.9, 129.1, 128.4, 127.7, 126.6, 117.1, 116.2, 112.3, 76.6, 54.0, 51.7, 50.0, 33.9, 32.4, 25.8, 24.8; IR (neat, ATR) 1745, 1600 $cm^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2120; Found 350.2125.

**Synthesis of Benzyl- and Allylglycine Derivatives via Aza-[1,2]- or [2,3]-Wittig Rearrangement.** *General Procedure 4.* A flame-dried flask was evacuated and backfilled with nitrogen three times and then charged with a 1 M solution of dibutylboron triflate in methylene chloride (1.5−3.2 equiv). The solution was diluted to ca. 0.5 M with methylene chloride and then cooled to 0 °C before Hünig's base (1.7−4.0 equiv) was added dropwise. A 1 M solution of the ester



DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

substrate (1.0 equiv) in methylene chloride was then added, and the resulting solution was warmed to 35 °C. After stirring for 2−4 h, the mixture was cooled to 0 °C, opened to air, and quenched by the addition of pH 7 buffer solution (ca. 3 mL/mmol substrate), methanol (ca. 6−8 mL/mmol substrate), and 30% aqueous $H_2O_2$ (ca. 1 mL/mmol substrate). This mixture was warmed to rt and stirred for 1 h. The solution was then cooled to 0 °C, and $Na_2S_2O_3$ (ca. 7 mL/mmol substrate) was added. This solution was allowed to stir for 1 min before it was diluted with water and extracted twice with $Et_2O$. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 5−10% diethyl ether in hexanes as the eluent.

*Methyl 3-Phenyl-2-(phenylamino)propanoate (**10a**).*[43] General procedure 4 was used for the rearrangement of **9a** (51 g, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 33 mg (65%) of the title compound as a colorless oil with spectroscopic properties identical to those previously reported.[43] $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.30−7.28 (m, 2 H), 7.25−7.23 (m, 1 H), 7.18−7.16 (m, 4 H), 6.74 (t, $J$ = 7.3 Hz, 1 H), 6.60 (d, $J$ = Hz, 2 H), 4.37 (t, $J$ = 6.3 Hz, 1 H), 4.16 (s, br, 1 H), 3.67 (s, 3 H), 3.16 (dd, $J$ = 13.7, 6.0 Hz, 1 H), 3.10 (dd, $J$ = 13.6, 6.5 Hz, 1 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.6, 146.3, 136.3, 129.4, 129.2, 128.5, 127.0, 118.4, 113.6, 57.7, 52.0, 38.6.

*Methyl 2-[(4-Bromophenyl)amino]-3-phenylpropanoate (**10b**).* General procedure 4 was used for the rearrangement of **9b** (67 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 39 mg (59%) of the title compound as an orange oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.30−7.23 (m, 5 H), 7.13 (d, $J$ = 6.9 Hz, 2 H), 6.47−6.44 (m, 2 H), 4.31 (t, $J$ = 6.3 Hz, 1 H), 4.16 (s, br, 1 H), 3.67 (s, 3 H), 3.14 (dd, $J$ = 6.1, 13.7 Hz, 1 H), 3.08 (dd, $J$ = 6.3, 13.7 Hz, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 173.2, 145.4, 136.0, 132.1, 129.2, 128.6, 127.1, 115.1, 110.1, 57.6, 52.1, 38.5; IR (neat, ATR) 3395,1736 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0432.

*Methyl 2-[(4-Methoxyphenyl)amino]-3-phenylpropanoate (**10c**).* General procedure 4 was used for the rearrangement of **9c** (50 mg, 0.18 mmol) with dibutylboron triflate (0.56 mL, 0.56 mmol) and $^{i}Pr_2NEt$ (0.12 mL, 0.7 mmol) in 0.18 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 35 mg (70%) of the title compound as an orange oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31−7.23 (m, 3 H), 7.17 (d, $J$ = 7.1 Hz, 2 H), 6.77−6.74 (m, 2 H), 6.59−6.56 (m, 2 H), 4.27 (t, $J$ = 6.4 Hz, 1 H), 3.88 (s, br, 1 H), 3.73 (s, 3 H), 3.64 (s, 3 H), 3.15−3.06 (m, 2 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.9, 152.9, 140.4, 136.5, 129.2, 128.5, 126.9, 115.3, 114.9, 59.0, 55.7, 52.0, 38.9; IR (neat, ATR) 3337,1684 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{20}NO_3$ 286.1443; Found 286.1438.

*Methyl 3-Phenyl-2-{[4-(trifluoromethyl)phenyl]amino}propanoate (**10d**).* General procedure 4 was used for the rearrangement of **9d** (97 mg, 0.3 mmol) with dibutylboron triflate (0.96 mL, 0.96 mmol) and $^{i}Pr_2NEt$ (0.21 mL, 1.2 mmol) in 0.3 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 23 mg (24%) of the title compound as a yellow oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.39 (d, $J$ = 8.4 Hz, 2 H), 7.32−7.22 (m, 3 H), 7.15−7.11 (m, 2 H), 6.59 (d, $J$ = 8.4 Hz, 2 H), 4.48 (d, $J$ = 8.4 Hz, 1 H), 4.42−4.39 (m, 1 H), 3.70 (s, 3 H), 3.18 (dd, $J$ = 13.7, 5.9 Hz, 1 H), 3.11 (dd, $J$ = 13.8, 6.2 Hz, 1 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 172.7, 148.8, 135.8, 129.2, 128.6, 127.2, 126.74, 126.71, 112.6, 57.0, 52.3, 38.3, 29.7; IR (neat, ATR) 3390, 1739 cm$^{-1}$. HRMS (ESI+) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{17}F_3NO_2$ 324.1211; Found 324.1206.

*Methyl 3-(4-Bromophenyl)-2-(phenylamino)propanoate (**10e**).* General procedure 4 was used for the rearrangement of **9e** (75 mg, 0.22 mmol) with dibutylboron triflate (0.72 mL, 0.72 mmol) and $^{i}Pr_2NEt$ (0.16 mL, 0.88 mmol) in 0.25 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 53 mg (70%) of the title compound as a yellow oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.40 (d, $J$ = 8.2 Hz, 2 H), 7.17 (t, $J$ = 5.5 Hz, 2 H), 7.02 (d, $J$ = 7.8 Hz, 2 H), 6.75 (td, $J$ = 1.1, 7.4 Hz, 1 H), 6.60 (d, $J$ = 8.5 Hz, 2 H), 4.37−4.34 (m, 1 H), 4.14 (d, $J$ = 8.3 Hz, 1 H), 3.67 (s, 3 H), 3.11 (dd, $J$ = 6.0, 13.7 Hz, 1 H), 3.04 (dd, $J$ = 6.2, 13.8 Hz, 1 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.2, 146.0, 135.3, 131.6, 131.0, 129.4, 121.0, 118.6, 113.5, 57.4, 52.2, 37.9; IR (neat, ATR) 3405, 1738 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0440.

*Methyl 3-(2-Bromophenyl)-2-(phenylamino)propanoate (**10f**).* General procedure 4 was used for the rearrangement of compound **9f** (67 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 31 mg (47%) of the title compound as a white solid, mp 100−102 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.55 (d, $J$ = 8.0 Hz, 1 H), 7.22−7.20 (m, 2 H), 7.13 (t, $J$ = 7.6 Hz, 2 H), 7.11−7.08 (m, 1 H), 6.72 (t, $J$ = 7.3 Hz, 1 H), 6.60 (d, $J$ = 7.8 Hz, 2 H), 4.45 (t, $J$ = 6.6 Hz, 1 H), 4.23 (s, br, 1 H), 3.63 (s, 3 H), 3.28 (dd, $J$ = 7.5, 13.6 Hz, 1 H), 3.21 (dd, $J$ = 7.8, 13.8 Hz, 1 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.7, 146.4, 136.3, 133.0, 131.4, 129.3, 128.7, 127.5, 124.8, 118.5, 113.6, 56.7, 52.1, 39.4; IR (neat, ATR) 3385,1736 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{17}BrNO_2$ 334.0443; Found 334.0438.

*Methyl 3-(Furan-2-yl)-2-(phenylamino)propanoate (**10g**).* General procedure 4 was used for the rearrangement of compound **9g** (49 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 36 mg (73%) of the title compound as a pale yellow solid, mp 66−68 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33 (d, $J$ = 1.6 Hz, 1 H), 7.17 (t, $J$ = 8.0 Hz, 2 H), 6.74 (t, $J$ = 7.3 Hz, 1 H), 6.60 (d, $J$ = 6.9 Hz, 2 H), 6.28 (dd, $J$ = 3.2, 1.9 Hz, 1 H), 6.10 (d, $J$ = 3.2 Hz, 1 H), 4.38 (dt, $J$ = 8.2, 5.9 Hz, 1 H), 4.24 (d, $J$ = 8.4 Hz, 1 H), 3.70 (s, 3 H), 3.17 (d, $J$ = 6.0 Hz, 2 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.3, 150.6, 146.3, 142.1, 129.3, 118.5, 113.6, 110.4, 107.8, 55.9, 52.2, 31.4; IR (neat, ATR) 3393, 1737 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{16}NO_3$ 246.1130; Found 246.1134.

*Methyl 2-(Phenylamino)-3-(thiophen-2-yl)propanoate (**10h**).* General procedure 4 was used for the rearrangement of compound **9h** (52 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 37 mg (70%) of the title compound as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.23−7.13 (m, 3 H), 6.94 (dd, $J$ = 5.2, 3.4 Hz, 1 H), 6.84 (d, $J$ = 3.4 Hz, 1 H), 6.67 (t, $J$ = 7.3 Hz, 1 H), 6.43 (d, $J$ = 7.5 Hz, 2 H), 4.41−4.37 (m, 1 H), 4.29 (d, $J$ = 8.8 Hz, 1 H), 3.73 (s, 3 H), 3.40 (dd, $J$ = 14.6, 5.3 Hz, 1 H), 3.33 (dd, $J$ = 14.8, 6.7 Hz, 1 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 173.0, 146.1, 137.9, 129.4, 126.9, 126.6, 124.8, 118.6, 113.7, 57.5, 52.3, 32.7; IR (neat, ATR) 3370,1732 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{16}NO_2S$ 262.0902; Found 262.0899.

*Methyl 2-(Phenylamino)-3-(1-tosyl-1H-pyrrol-2-yl)propanoate (**10i**).* General procedure 4 was used for the rearrangement of compound **9i** (65 mg, 0.163 mmol) with dibutylboron triflate (0.52 mL, 0.521 mmol) and $^{i}Pr_2NEt$ (0.11 mL, 0.652 mmol) in 0.15 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 36 mg (59%) of the title compound as a pale yellow oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.63 (d, $J$ = 8.4 Hz, 2 H), 7.29 (dd, $J$ = 3.4, 1.7 Hz, 1 H), 7.25 (d, $J$ = 8.2 Hz, 2 H), 7.20−7.11 (m, 2 H), 6.72 (t, $J$ = 7.3 Hz, 1 H), 6.56 (d, $J$ = 7.9 Hz, 2 H), 6.19 (t, $J$ = 3.3 Hz, 1 H), 6.09 (dd, $J$ = 3.4, 1.7 Hz, 1 H), 4.36 (q, $J$ = 7.0 Hz, 1 H), 4.20 (s, br, 1 H), 3.63 (s, 3 H), 3.22 (dd, $J$ = 15.1, 7.4 Hz, 1 H),


DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

3.17 (dd, $J$ = 15.2, 6.6 Hz, 1 H), 2.38 (s, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.8, 146.4, 145.1, 136.2, 130.1, 129.9, 129.3, 126.6, 123.4, 118.4, 115.0, 113.5, 111.8, 56.8, 52.1, 31.0, 21.6; IR (neat, ATR) 3370,1736, 1601, 1362 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{21}H_{23}N_2O_4S$ 399.1379; Found 399.1379.

*Methyl 3-Phenyl-2-(phenylamino)butanoate (**12**).* General procedure 4 was used for the rearrangement of **11** (48 mg, 0.18 mmol) with dibutylboron triflate (0.58 mL, 0.58 mmol) and $^i$Pr$_2$NEt (0.13 mL, 0.72 mmol) in 0.2 mL of dichloromethane. The crude product was purified using flash column chromatography with 90% hexanes/diethyl ether as the eluent. This procedure afforded 32 mg (66%) of the title compound as a white solid, mp 55−57 °C. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1.6:1 dr following purification. Data are for the mixture. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.37−7.20 (m, 5 H), 7.12 (t, $J$ = 7.6 Hz, 2 H), 6.73−6.69 (m, 1 H), 6.58−6.54 (m, 2 H), 4.22−4.17 (m, 1.4 H), 3.90 (d, $J$ = 8.7 Hz, 0.6 H), 3.68 (s, 1.8 H), 3.49 (s, 1.2 H), 3.32−3.29 (m, 0.6 H), 3.22−3.20 (m, 0.4 H), 1.46 (d, $J$ = 7.2 Hz, 1.2 H), 1.40 (d, $J$ = 7.1 Hz, 1.8 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.9, 147.1, 142.0, 129.3, 128.6, 127.8, 127.2, 118.5, 113.8, 63.1, 52.0, 43.0, 18.4; IR (neat, ATR) 3387, 1734 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{17}H_{20}NO_2$ 270.1494; Found 270.1480.

*Methyl-2-(phenylamino)pent-4-enoate (**15a**).* General procedure 4 was used for the reaction of compound **14a** (41 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 29 mg (70%) of the title compound as a pale yellow oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.19−7.14 (m, 2 H), 6.74 (t, $J$ = 7.4 Hz, 1 H), 6.63−6.59 (m, 2 H), 5.78 (ddt, $J$ = 17.2, 10.1, 7.2 Hz, 1 H), 5.19−5.13 (m, 2 H), 4.15 (s, 1 H), 3.72 (s, 3 H), 2.64−2.53 (m, 2 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.9, 146.5, 132.7, 129.3, 119.0, 118.4, 113.4, 56.0, 52.1, 37.0; IR (neat, ATR) 3400, 1737, 1603 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$ 206.1181; Found 206.1171.

*(2S*,3R*)-Methyl-3-methyl-2-(phenylamino)pent-4-enoate (**15b**).* General procedure 4 was used for the reaction of compound **14b** (44 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 26 mg (59%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.19−7.14 (m, 2 H), 6.76−6.71 (m, 1 H), 6.64−6.58 (m, 2 H), 5.76 (ddd, $J$ = 17.6, 10.2, 8.4 Hz, 1 H), 5.19−5.08 (m, 2 H), 4.15 (d, $J$ = 9.6 Hz, 1 H), 4.01 (dd, $J$ = 9.4, 5.8 Hz, 1 H), 3.69 (s, 3 H), 2.67−2.64 (m, 1 H), 1.16 (d, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.4, 146.9, 139.1, 129.3, 118.4, 116.5, 113.6, 61.1, 51.8, 41.4, 16.5; IR (neat, ATR) 3396, 1735, 1602 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$ 220.1338; Found 220.1335.

*(2S*,3S*)-Methyl-3-phenyl-2-(phenylamino)pent-4-enoate (**15c**).* General procedure 4 was used for the reaction of compound **14c** (56.3 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 41 mg (73%) of a 4:1 mixture of **15c** and **15c′**, a product resulting from the aza-[1,2]-Wittig rearrangement. After a second careful chromatography, small amounts of each pure compound were isolated for characterization.

*Title Compound **15c**.* White solid, mp 71−74 °C. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.30 (m, 2 H), 7.32−7.19 (m, 3 H), 7.21−7.10 (m, 2 H), 6.73 (t, $J$ = 7.3 Hz, 1 H), 6.60 (d, $J$ = 7.8 Hz, 2 H), 6.15 (ddd, $J$ = 16.9, 10.1, 9.0 Hz, 1 H), 5.26−5.16 (m, 2 H), 4.38 (t, $J$ = 7.6 Hz, 1 H), 3.99 (d, $J$ = 8.1 Hz, 1 H), 3.79 (t, $J$ = 8.1 Hz, 1 H), 3.65 (s, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 173.2, 146.6, 139.2, 136.8, 129.2, 128.8, 127.9, 127.3, 118.6, 117.7, 113.7, 61.3, 53.2, 51.8; IR (neat, ATR) 3384, 1737, 1601 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{20}NO_2$ 282.1494; Found 282.1491.

*Side Product (E)-Methyl 5-Phenyl-2-(phenylamino)pent-4-enoate (**15c′**).* $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.36−7.13 (m, 7 H), 6.78−6.74 (m, 1 H), 6.64 (d, $J$ = 8.0 Hz, 2 H), 6.51 (d, $J$ = 15.7 Hz, 1 H), 6.17−6.14 (m, 1 H), 4.26−4.24 (m, 2 H), 3.74 (s, 3 H), 2.81−2.71 (m, 2 H).

*Methyl-3,3-dimethyl-2-(phenylamino)pent-4-enoate (**15d**).* General procedure 4 was used for the reaction of compound **14d** (47 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 35 mg (75%) of a 2:1 mixture of **15d** and **15d′**, a product resulting from the aza-[1,2]-Wittig rearrangement. After a second careful chromatography, small amounts of each pure compound were isolated for characterization. Title Compound **15d**: White solid, mp 45−47 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.14 (dd, $J$ = 7.2, 8.5 Hz, 2 H), 6.71 (t, $J$ = 7.3 Hz, 1 H), 6.64−6.56 (m, 2 H), 5.94 (dd, $J$ = 17.4, 10.8 Hz, 1 H), 5.20−5.06 (m, 2 H), 4.09 (d, $J$ = 9.9 Hz, 1 H), 3.84 (d, $J$ = 9.8 Hz, 1 H), 3.66 (s, 3 H), 1.16 (d, $J$ = 13.7 Hz, 6 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.4, 147.2, 143.2, 129.3, 118.3, 114.2, 113.6, 64.6, 51.6, 40.2, 24.9, 23.7; IR (neat, ATR) 3384, 1736, 1603 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$ 234.1494; Found 234.1488.

*Side Product Methyl-5-methyl-2-(phenylamino)hex-4-enoate (**15d′**).* $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.20−7.11 (m, 2 H), 6.71 (t, $J$ = 7.3 Hz, 1 H), 6.59 (d, $J$ = 8.0 Hz, 2 H), 5.11 (t, $J$ = 7.5 Hz, 1 H), 4.08 (t, $J$ = 6.1 Hz, 1 H), 3.70 (s, 3 H), 2.61−2.44 (m, 2 H), 1.71 (s, 3 H), 1.60 (s, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 174.2, 146.7, 136.0, 129.3, 118.2, 118.1, 113.4, 56.5, 52.1, 31.4, 25.9, 17.9; IR (neat, ATR) 3369, 1738, 1604 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{20}NO_2$ 234.1489; Found 234.1486.

*Methyl-4-methyl-2-(phenylamino)pent-4-enoate (**15e**).* General procedure 4 was used for the reaction of compound **14e** (44 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 24 mg (55%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.24−7.13 (m, 2 H), 6.74 (t, $J$ = 7.3 Hz, 1 H), 6.64−6.58 (m, 2 H), 4.89 (s, 1 H), 4.83 (s, 1 H), 4.17 (q, $J$ = 6.7 Hz, 1 H), 4.06 (s, br, 1 H), 3.71 (s, 3 H), 2.58 (dd, $J$ = 6.1, 13.8 Hz, 1 H), 2.50 (dd, $J$ = 8.2, 13.8 Hz, 1 H), 1.76 (s, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 174.4, 146.6, 140.7, 129.3, 118.4, 114.5, 113.3, 55.0, 52.1, 41.2, 21.8; IR (neat, ATR) 3318, 1738, 1603 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{18}NO_2$ 220.1338; Found 220.1325.

*(2S*,3R*)-Methyl-2-[(4-methoxyphenyl)amino]-3-vinyloctanoate (**15f**).* General procedure 4 was used for the reaction of compound **14f** (62 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 36 mg (58%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 6.79−6.70 (m, 2 H), 6.63−6.52 (m, 2 H), 5.66−5.57 (m, 1 H), 5.21−5.05 (m, 2 H), 3.97−3.91 (m, 2 H), 3.73 (s, 3 H), 3.66 (s, 3 H), 2.42−2.38 (m, 1 H), 1.64−1.59 (m, 1 H), 1.43−1.26 (m, 7 H), 0.88 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.7, 152.8, 141.0, 137.8, 118.1, 115.3, 114.9, 61.4, 55.7, 51.6, 47.7, 31.7, 30.9, 26.8, 22.5, 14.0; IR (neat, ATR) 3394, 1735, 1512 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{28}NO_3$ 306.2069; Found 306.2062.

*(2S*,3R*)-Methyl-2-[(4-chlorophenyl)amino]-3-ethylpent-4-enoate (**15g**).* General procedure 4 was used for the reaction of compound **14g** (56.3 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 35 mg (62%) of the title compound as a colorless oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.12−7.07 (m, 2 H), 6.56−6.49 (m, 2 H), 5.61−5.56 (m, 1 H), 5.20−5.12 (m, 2 H), 4.18 (d, $J$ = 10.0 Hz, 1 H), 4.00 (dd, $J$ = 5.9, 10.0 Hz, 1 H), 3.67 (s, 3 H), 2.34−2.31



DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

(m, 1 H), 1.69−1.62 (m, 1 H), 1.40−1.31 (m, 1 H), 0.91 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.1, 145.4, 137.1, 129.2, 123.0, 118.8, 114.7, 59.9, 51.8, 49.4, 24.0, 11.8; IR (neat, ATR) 3394, 1734, 1600 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{19}ClNO_2$ 268.1104; Found 268.1094.

*(2S*,1′S*)-Methyl-2-(2′-methylenecyclohexyl)-2-(phenylamino)-acetate (**15h**).* General procedure 4 was used for the reaction of compound **14h** (70 mg, 0.27 mmol) with dibutylboron triflate (0.4 mL, 0.4 mmol) and $^i$Pr$_2$NEt (0.08 mL, 0.46 mmol) in 1.0 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 39 mg (56%) of the title compound as a white solid, mp 65−71 °C. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 2:1 dr following purification. Data are for the mixture. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.20−1.14 (m, 2 H), 6.76−6.71 (m, 1 H), 6.66 (d, $J$ = 8.0 Hz, 1.25 H), 6.60 (d, $J$ = 8.0 Hz, 0.75 H), 4.86 (s, 0.38 H), 4.82 (s, 0.38 H), 4.73 (s, 0.62 H), 4.66 (s, 0.62 H), 4.32 (d, $J$ = 9.4 Hz, 0.62 H), 4.12 (d, $J$ = 9.9 Hz, 0.38 H), 3.74 (s, 1.14 H), 3.62 (s, 1.86 H), 2.59−2.52 (m, 1 H), 2.35−2.27 (m, 0.75 H), 2.21−2.07 (m, 2.25 H), 1.75−1.43 (m, 5 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 174.4, 148.2, 147.1, 129.4, 129.3, 118.5, 118.2, 113.5, 113.0, 110.3, 109.7, 76.2, 57.7, 57.3, 52.1, 51.6, 47.2, 46.3, 33.0, 29.9, 28.5, 28.2, 28.0, 27.9, 22.6, 22.2 (two carbon signals missing due to incidental overlap); IR (neat, ATR) 3385, 1737, 1603 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{22}NO_2$ 260.1651; Found 260.1642.

*Methyl-3-phenyl-2-(phenylamino)pent-4-enoate (**20**).* General procedure 4 was used for the reaction of **17** (44.0 mg, 0.2 mmol) with dibutylboron triflate (0.3 mL, 0.3 mmol) and $^i$Pr$_2$NEt (0.06 mL, 0.34 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 8.5 mg (21%) of the title compound as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.29−7.16 (m, 2 H), 6.89−6.76 (m, 2 H), 5.99−5.92 (m, 1 H), 5.27−5.00 (m, 2 H), 4.45 (q, $J$ = 7.2 Hz, 1 H), 4.06−3.96 (m, 2 H), 1.52 (d, $J$ = 7.2 Hz, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 178.1, 148.3, 135.7, 129.3, 129.1, 118.7, 116.3, 114.6, 57.2, 51.0, 15.3; IR (neat, ATR) 1711, 1599 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{16}NO_2$ 206.1181; Found 206.1176.

*(1S,2R)-2-Phenylcyclohexyl 3-Phenyl-2-(phenylamino)propanoate (**22a**).* General procedure 4 was used for the rearrangement of **22a** (80 mg, 0.2 mmol) with dibutylboron triflate (0.64 mL, 0.64 mmol) and $^i$Pr$_2$NEt (0.14 mL, 0.8 mmol) in 0.2 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 68 mg (85%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1.6:1 dr following purification. Data are for the mixture. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.35−7.09 (m, 8 H), 7.08 (t, $J$ = 7.9 Hz, 1.2 H), 7.04 (d, $J$ = 7.2 Hz, 0.8 H), 7.00 (t, $J$ = 7.7 Hz, 0.8 H), 6.79−6.63 (m, 2.2 H), 6.42 (d, $J$ = 8.0 Hz, 1.2 H), 6.23 (d, $J$ = 8.0 Hz, 0.8 H), 5.00−4.92 (m, 1 H), 4.11−4.09 (m, 0.6 H), 3.96−3.94 (m, 0.4 H), 3.88 (d, $J$ = 7.5 Hz, 1 H), 2.88 (dd, $J$ = 12.4, 6.1 Hz, 0.4 H), 2.81 (dd, $J$ = 13.9, 7.1 Hz, 0.4 H), 2.74 (td, $J$ = 12.6, 3.7 Hz, 0.6 H), 2.68−2.60 (m, 1 H), 2.45 (dd, $J$ = 14.0, 6.9 Hz, 0.6 H), 2.15−2.13 (m, 0.6 H), 1.97−1.91 (m, 1 H), 1.85−1.83 (m, 0.4 H), 1.80−1.74 (m, 1 H), 1.87−1.63 (m, 5 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 172.4, 146.5, 146.3, 143.1, 136.4, 129.3, 129.2, 128.5, 128.4, 127.7, 126.9, 118.1, 113.5, 77.6, 57.5, 49.8, 38.5, 33.9, 32.4, 25.8, 24.7; IR (neat, ATR) 3396, 1731 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{27}H_{30}NO_2$ 400.2277; Found 400.2284.

*(1S,2R)-2-Phenylcyclohexyl 2-[Benzyl(phenyl)-λ$^4$-azanyl]acetate (**22b**).* General procedure 3 was used for the reaction of compound **21b** (49 mg, 0.14 mmol) with dibutylboron triflate (0.21 mL, 0.21 mmol) and $^i$Pr$_2$NEt (0.04 mL, 0.24 mmol) in 0.5 mL of dichloromethane. The crude product was purified using flash column chromatography with 95% hexanes/diethyl ether as the eluent. This procedure afforded 31 mg (64%) of the title compound as a colorless oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1.3:1 dr following purification. Data are for the mixture. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.33−7.16 (m, 5 H), 7.12−7.08 (m, 1.12 H), 7.04−7.01 (m, 0.87 H), 6.69 (dt, $J$ = 7.3, 12.5 Hz, 1 H), 6.49 (d, $J$ = 8.0 Hz, 1.12 H), 6.27 (d, $J$ = 8.0 Hz, 0.87 H), 5.48−5.42 (m, 0.44 H), 5.15−4.97 (m, 2.43 H), 4.89−4.78 (m, 1.12 H), 3.95 (s, br, 1 H), 3.88 (t, $J$ = 5.7 Hz, 0.56 H), 3.78 (t, $J$ = 6.1 Hz, 0.44 H), 2.73−2.66 (m, 1H), 2.36−2.31 (m, 1 H), 2.16−1.77 (m, 5 H), 1.59−1.28 (m, 4 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 172.5, 172.4, 146.5, 146.4, 143.0, 132.7, 132.6, 129.2, 129.1, 128.5, 128.4, 127.5, 127.4, 126.6, 126.5, 118.8, 118.5, 118.2, 118.0, 113.4, 113.2, 77.1, 76.9, 55.6, 55.5, 49.9, 49.7, 36.8, 36.3, 34.1, 34.0, 32.4, 32.1, 25.8, 25.7, 24.7, 24.6 (one carbon signal missing due to incidental overlap); IR (neat, ATR) 3416, 1734, 1603 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{23}H_{28}NO_2$ 350.2120; Found 350.2113.

**Synthesis and Characterization of [2,3] Rearrangement/Hydroboration Products.** *General Procedure 5.* A flame-dried flask was evacuated and backfilled with nitrogen three times and then charged with a 1 M solution of dibutylboron triflate in methylene chloride (1.5−2.0 equiv). The solution was cooled to 0 °C, and Hünig's base (4.0 equiv) was added dropwise. A 1 M solution of the ester substrate (1.0 equiv) in methylene chloride was then added, and the resulting solution was warmed to 35−40 °C. After stirring for 2 h, the mixture was cooled to 0 °C, and additional $Bu_2BOTf$ (2.0 equiv, 1 M solution in $CH_2Cl_2$) was added. The reaction was heated to 40 °C and allowed to stir for 4 h. The flask was then cooled to 0 °C, opened to air, and quenched by the addition of pH 7 buffer solution (ca. 3 mL/mmol substrate), methanol (ca. 6−8 mL/mmol substrate), and 30% aqueous $H_2O_2$ (ca. 1 mL/mmol substrate). This mixture was warmed to rt and stirred for 1 h. The solution was then cooled to 0 °C, and $Na_2S_2O_3$ (ca. 7 mL/mmol substrate) was added. This solution was allowed to stir for 1 min before it was diluted with water and extracted twice with $Et_2O$. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel using 30−40% ethyl acetate in hexanes as the eluent.

*Methyl-5-hydroxy-2-(phenylamino)pentanoate (**16a**).* General procedure 5 was used for the reaction of compound **14a** (41 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and $^i$Pr$_2$NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 24 mg (54%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.17 (t, $J$ = 7.4 Hz, 2 H), 6.75 (t, $J$ = 7.2 Hz, 1 H), 6.62 (d, $J$ = 7.7 Hz, 2 H), 4.11 (dd, $J$ = 5.4, 7.0 Hz, 1 H), 3.72 (s, 3 H), 3.67 (t, $J$ = 6.0 Hz, 2 H), 2.01−1.80 (m, 2 H), 1.74−1.67 (m, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 174.6, 146.7, 129.4, 118.6, 113.6, 62.2, 56.6, 52.2, 29.7, 28.8; IR (neat, ATR) 3382, 1732 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{12}H_{18}NO_3$ 224.1287; Found 224.1288.

*(2S*,3R*)-Methyl-5-hydroxy-3-methyl-2-(phenylamino)pentanoate (**16b**).* General procedure 5 was used for the reaction of compound **14b** (44 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and $^i$Pr$_2$NEt (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 26 mg (55%) of the title compound as a colorless oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.17 (t, $J$ = 7.4 Hz, 2 H), 6.75 (t, $J$ = 7.4 Hz, 1 H), 6.64 (d, $J$ = 7.8 Hz, 2 H), 4.06 (d, $J$ = 4.5 Hz, 1 H), 3.81−3.64 (m, 5 H), 2.31−2.20 (m, 1 H), 1.83−1.74 (m, 1 H), 1.59−1.51 (m, 1 H), 1.03 (d, $J$ = 7.0 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 174.1, 147.2, 129.4, 118.6, 113.9, 60.9, 60.4, 52.1, 36.2, 33.0, 15.3; IR (neat, ATR) 3388, 1731 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{20}NO_3$ 238.1443; Found 238.1445.

*(2S*,3S*)-Methyl-5-hydroxy-3-phenyl-2-(phenylamino)pentanoate (**16c**).* General procedure 5 was used for the reaction of



DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

compound **14c** (56 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 34 mg (57%) of the title compound as a colorless oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.33−7.24 (m, 3 H), 7.19 (d, $J$ = 7.0 Hz, 2 H), 7.12 (t, $J$ = 7.4 Hz, 2 H), 6.71 (t, $J$ = 7.4 Hz, 1 H), 6.58 (d, $J$ = 7.9 Hz, 2 H), 4.32 (d, $J$ = 6.0 Hz, 1 H), 3.90 (s, br, 1 H), 3.66 (s, 3 H), 3.63−3.57 (m, 1 H), 3.49−3.37 (m, 2 H), 2.10−2.05 (m, 2 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 173.6, 147.1, 139.0, 129.3, 128.7, 128.3, 127.5, 118.6, 113.8, 61.5, 60.5, 52.0, 45.1, 34.9; IR (neat, ATR) 3388, 1731 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{22}NO_3$ 300.1600; Found 300.1600.

*Methyl-5-hydroxy-3,3-dimethyl-2-(phenylamino)pentanoate (**16d**).* General procedure 5 was used for the reaction of compound **14d** (47 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 23 mg (45%) of the title compound as a yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.22−7.10 (m, 2 H), 6.75 (t, $J$ = 7.3 Hz, 1 H), 6.73−6.62 (m, 2 H), 3.96 (s, 1 H), 3.81−3.72 (m, 2 H), 3.66 (s, 3 H), 1.70 (t, $J$ = 6.7 Hz, 2 H), 1.06 (d, $J$ = 5.9 Hz, 6 H). $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 174.0, 147.1, 129.4, 119.0, 114.3, 64.6, 59.1, 51.7, 42.6, 36.4, 25.4, 23.8; IR (neat, ATR) 3388, 1730, 1602 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{22}NO_3$ 252.1600; Found 252.1599.

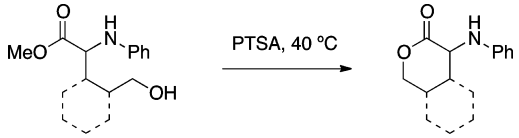
*Methyl-5-hydroxy-4-methyl-2-(phenylamino)pentanoate (**16e**).* General procedure 5 was used for the reaction of compound **14e** (44 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 24 mg (51%) of the title compound as a pale yellow oil. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 1:1 dr following purification. Data are for the mixture. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.23−7.13 (m, 2 H), 6.76 (td, $J$ = 3.7, 7.3 Hz, 1 H), 6.65 (dd, $J$ = 3.3, 7.5 Hz, 2 H), 4.20−4.17 (m, 1 H), 4.14−4.11 (m, 1 H), 3.70 (d, $J$ = 5.9 Hz, 3 H), 3.61−3.44 (m, 2 H), 1.99−1.79 (m, 2 H), 1.72−1.67 (m, 1 H), 1.02 (d, $J$ = 6.8 Hz, 1.5 H), 0.97 (d, $J$ = 6.8 Hz, 1.5 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 175.1, 146.8, 129.4, 118.9, 118.8, 114.0, 113.8, 68.0, 67.5, 55.6, 55.0, 52.2, 52.1, 37.6, 37.1, 33.3, 32.6, 17.0, 16.9 (three carbon signals are missing due to incidental equivalence); IR (neat, ATR) 3372, 1733, 1601 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{13}H_{20}NO_3$ 238.1443; Found 238.1438.

*(2S*,3R*)-Methyl-3-(2-hydroxyethyl)-2-[(4-methoxyphenyl)amino]octanoate (**16f**).* General procedure 5 was used for the reaction of compound **14f** (61 mg, 0.2 mmol) with dibutylboron triflate (0.7 mL, 0.7 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 28 mg (44%) of the title compound as a pale yellow oil. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.78−6.75 (m, 2 H), 6.66−6.64 (m, 2 H), 4.06 (d, $J$ = 4.1 Hz, 1 H), 3.77−3.63 (m, 8 H), 2.08−2.03 (m, 1 H), 1.80−1.64 (m, 2 H), 1.45−1.23 (m, 8 H), 0.90 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 174.4, 153.2, 140.9, 116.1, 114.8, 61.3, 60.3, 55.6, 52.0, 38.6, 33.8, 31.9, 29.6, 26.8, 22.5, 14.0; IR (neat, ATR) 3397, 1732, 1512 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{18}H_{30}NO_4$ 324.2175; Found 324.2172.

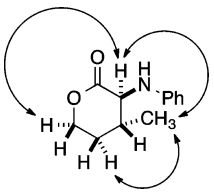
*(2S*,3R*)-Methyl-2-[(4-chlorophenyl)amino]-3-ethyl-5-hydroxypentanoate (**16g**).* General procedure 5 was used for the reaction of compound **14g** (56 mg, 0.2 mmol) with dibutylboron triflate (0.8 mL, 0.7 mmol) and $^{i}Pr_2NEt$ (0.14 mL, 0.8 mmol) in 0.7 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 27 mg (48%) of the title compound as a yellow oil. $^1$H NMR (700 MHz, $CDCl_3$) $\delta$ 7.13−7.08 (m, 2 H), 6.57−6.52 (m, 2 H), 4.31 (s, br, 1 H), 4.10 (d, $J$ = 4.5 Hz, 1 H), 3.77−3.75 (m, 1 H), 3.70 (s, 3 H), 3.68−3.65 (m, 1 H), 2.00−1.97 (m, 1 H), 1.75−1.66 (m, 1 H), 1.64−1.59 (m, 1 H), 1.54−1.49 (m, 1 H), 1.47−1.38 (m, 1 H), 0.97 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 173.9, 145.7, 129.2, 123.2, 114.8, 60.8, 59.2, 52.1, 40.0, 33.0, 23.1, 11.6; IR (neat, ATR) 3402, 3336, 1728, 1600 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{14}H_{21}ClNO_3$ 286.1210; Found 286.1203.

*(2S*,1S,2′S)-Methyl-2-[2′-(hydroxymethyl)cyclohexyl]-2-(phenylamino)acetate (**16h**).* General procedure 5 was used for the reaction of compound **14h** (72 mg, 0.28 mmol) with dibutylboron triflate (0.95 mL, 0.95 mmol) and $^{i}Pr_2NEt$ (0.19 mL, 1.1 mmol) in 1.0 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 29 mg (38%) of the title compound as a yellow solid, mp 90−93 °C. The diastereoselectivity of the transformation could not be determined through $^1$H NMR analysis of the crude reaction mixture prior to purification due to signal overlap with boron-containing byproducts; the isolated product was obtained with 3:1 dr following purification. Data are for the mixture. $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.22−7.14 (m, 2 H), 6.80 (t, $J$ = 7.3 Hz, 1 H), 6.74−6.64 (m, 2 H), 4.15 (d, $J$ = 26.1 Hz, 1 H), 4.07−3.95 (m, 1 H), 3.68 (s, 3 H), 3.60 (dd, $J$ = 11.6, 5.6 Hz, 1 H), 2.12−1.98 (m, 2 H), 1.82 (s, 2 H), 1.78−1.71 (m, 1 H), 1.53−1.25 (m, 5 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 174.9, 172.9, 147.4, 146.5, 1294, 129.3, 119.4, 118.6, 114.6, 113.8, 72.2, 62.8, 59.4, 55.2, 51.8, 41.5, 39.0, 38.5, 34.4, 29.7, 27.8, 26.7, 26.6, 25.0, 24.7, 23.4, 22.6, 21.4; IR (neat, ATR) 3381, 1730, 1602 cm$^{-1}$. HRMS (ESI+, magnetic sector) $m/z$: $[M + H]^+$ calcd for $C_{16}H_{24}NO_3$ 278.1756; Found 278.1752.

**Determination of Stereochemistry.** The relative stereochemistry of compounds **15b** and **15h** was assigned via 1D NOESY analysis of lactones **23** and **24**, which were generated via lactonization as described below. The stereochemistry of **15c**, **15f**, and **15g** was assigned based on analogy to **15b** and **15h**.



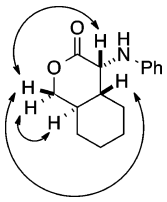

*General Procedure 6.* A flame-dried flask was evacuated and backfilled with nitrogen three times and then charged with a 1 M solution of the [2,3] rearrangement product **15** in methylene chloride. To this solution was added *p*-toluenesulfonic acid (1 equiv). The solution was heated to 40 °C until the cyclization was complete, as judged by TLC analysis. The mixture was then cooled to rt, quenched with saturated sodium bicarbonate, and extracted twice with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 30−40% ethyl acetate in hexanes on silica gel.




*(3S*,4R*)-4-Methyl-3-(phenylamino)tetrahydro-2H-pyran-2-one (**23**).* General procedure 6 was used for the reaction of **15b** (26 mg, 0.11 mmol) with *p*-toluenesulfonic acid (21 mg, 0.11 mmol) in 1.1 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 10 mg (45%) of the title compound as a pale yellow oil. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.22−7.11 (m, 2 H), 6.75 (t, $J$ = 7.3 Hz, 1 H), 6.67 (d, $J$ = 7.9 Hz, 2 H), 4.45−4.27 (m, 2 H), 4.10 (s, br, 1 H), 3.75 (d, $J$ = 10.9 Hz, 1 H), 2.26−2.17 (m, 1 H), 2.05−1.98 (m, 1 H), 1.76−1.69 (m, 1 H), 1.25 (d, $J$ = 6.7 Hz, 3 H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$ 173.4, 147.8, 129.3, 118.8, 113.9, 66.1,


DOI: 10.1021/acs.joc.5b01286
J. Org. Chem. 2015, 80, 9041−9056

59.5, 33.8, 30.1, 20.3; IR (neat, ATR) 1746 $cm^{-1}$. HRMS (ESI+) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{16}NO_2$ 206.1181; Found 206.1171.




*(4S*,4aR*,8aR*)-4-(Phenylamino)hexahydro-1H-isochromen-3(4H)-one (**24**).* General procedure 6 was used for the reaction of **15h** (29 mg, 0.11 mmol) with *p*-toluenesulfonic acid (20 mg, 0.11 mmol) in 1.1 mL of dichloromethane. The crude product was purified using flash column chromatography with 70% hexanes/ethyl acetate as the eluent. This procedure afforded 10 mg (39%) of the title compound as a white solid, mp 110−112 °C. $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.15 (dd, $J$ = 7.3, 8.6 Hz, 2 H), 6.67 (t, $J$ = 7.3 Hz, 1 H), 6.65 (d, $J$ = 8.0 Hz, 2 H), 4.32 (dd, $J$ = 3.2, 11.5 Hz, 1 H), 4.25 (dd, $J$ = 5.4, 11.2 Hz, 1 H), 4.02 (d, $J$ = 8.9 Hz, 1 H), 3.84 (s, br, 1 H), 3.59 (s, 2 H), 2.06−1.95 (m, 2 H), 1.79−1.39 (m, 8 H); $^{13}$C NMR (176 MHz, $CDCl_3$) $\delta$ 1728, 147.4, 129.3, 118.6, 113.8, 72.1, 55.3, 38.5, 34.3, 26.6, 25.0, 23.4, 21.4; IR (neat, ATR) 3384, 1730, 1602 $cm^{-1}$. HRMS (ESI+) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{20}NO_2$ 246.1494; Found 246.1489.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01286.

Copies of $^1$H and $^{13}$C NMR spectra for all substrates and products (PDF)

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail: jpwolfe@umich.edu.

### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

The authors thank the NSF (CHE 1111218) for financial support of this work.

## ■ REFERENCES

(1) Wittig, G.; Lohmann, L. *Justus Liebigs Ann. Chem.* **1942**, *550*, 260.
(2) For selected reviews, see: (a) Tomooka, K.; Yamamoto, H.; Nakai, T. *Liebigs Ann./Recueil* **1997**, *1997*, 1275. (b) Nakai, T.; Mikami, K. *Chem. Rev.* **1986**, *86*, 885.
(3) Bertrand, M. B.; Wolfe, J. P. *Org. Lett.* **2006**, *8*, 4661.
(4) Giampietro, N. C.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12556.
(5) Giampietro, N. C.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2010**, *49*, 2922.
(6) A portion of this work has been previously communicated. See: Everett, R. K.; Wolfe, J. P. *Tetrahedron Lett.* **2015**, *56*, 3393.
(7) For a review on the aza-Wittig rearrangement, see: Vogel, C. *Synthesis* **1997**, *1997*, 497.
(8) (a) Coldham, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1275. (b) Tomoyasu, T.; Tomooka, K. *Synlett* **2004**, 1925. (c) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817. (d) Murata, Y.; Nakai, T. *Chem. Lett.* **1990**, 2069.
(9) Katritzky, A. R.; Luo, Z.; Fang, Y.; Feng, D.; Ghiviriga, I. *J. Chem. Soc. Perkin Trans. 2* **2000**, 1375.
(10) (a) Ahman, J.; Somfai, P. *J. Am. Chem. Soc.* **1994**, *116*, 9781. (b) Åhman, J.; Somfai, P. *Tetrahedron* **1995**, *51*, 9747.
(11) (a) Anderson, J. C.; Flaherty, A.; Swarbrick, M. E. *J. Org. Chem.* **2000**, *65*, 9152. (b) Anderson, J. C.; Davies, E. A. *Tetrahedron* **2010**, *66*, 6300. (c) Anderson, J. C.; O'Loughlin, J. M. A.; Tornos, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2741.
(12) Coldham, I.; Middleton, M. L.; Taylor, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2817.
(13) (a) Blid, J.; Brandt, P.; Somfai, P. *J. Org. Chem.* **2004**, *69*, 3043. (b) Blid, J.; Panknin, O.; Somfai, P. *J. Am. Chem. Soc.* **2005**, *127*, 9352.
(14) Use of $Bu_2BOTf$ as a Lewis acid (along with a strong base) failed to promote rearrangement under these conditions. See ref 13a.
(15) For other examples of related 1,4,2-oxazaborole derivatives, see: (a) Ishikura, M.; Kato, H. *Tetrahedron* **2002**, *58*, 9827. (b) Pelter, A.; Smith, K.; Hutchings, M. G.; Rowe, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 129. (c) Pelter, A.; Hutchings, M. G.; Rowe, K.; Smith, K. *J. Chem. Soc., Perkin Trans. 1* **1975**, 138. (d) Denniel, V.; Bauchat, P.; Toupet, L.; Carboni, B.; Danion, D.; Danion-Bougot, R. *Tetrahedron Lett.* **1995**, *36*, 3507. (e) Denniel, V.; Bauchat, P.; Carboni, B.; Danion, D.; Danion-Bougot, R. *Tetrahedron Lett.* **1995**, *36*, 6875.
(16) For recent reviews on Suzuki coupling, see: (a) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 412. (b) Amatore, C.; Le Duc, G.; Jutand, A. *Chem. - Eur. J.* **2013**, *19*, 10082. (c) Lennox, A. J. J.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2013**, *52*, 7362. (d) Martin, R.; Buchwald, S. L. *Acc. Chem. Res.* **2008**, *41*, 1461.
(17) We have elected to classify this as a Wittig-type rearrangement as it does not appear that an ammonium ion resulting from protonation of the amino group (as in a Stevens-type rearrangement) is required. However, there likely is a Lewis acid/base chelate interaction between the O-$BR_2$ group and the amino group in the intermediate enolate, so in this case, there may not be a clean division between classification as a Wittig rearrangement vs a Stevens rearrangement.
(18) Treatment of **9a** with $Bu_2BOTf$ and $^i$Pr$_2$NEt at rt for 15 min, followed by quenching with $D_2O$, led to the formation of **10a** with ca. 50% D-incorporation at the carbon adjacent to the carbonyl, which indicates that formation of the enolate derived from **10a** does occur under these conditions.
(19) For examples of retro-hydroboration/dehydroboration, see: (a) Brown, H. C.; Negishi, E.; Katz, J. J. *J. Am. Chem. Soc.* **1972**, *94*, 5893. (b) Xu, B.-H.; Mömming, C. M.; Fröhlich, R.; Kehr, G.; Erker, G. *Chem. - Eur. J.* **2012**, *18*, 1826. (c) Heinz Karsch, H.; Hanika, G.; Huber, B.; Riede, J.; Müller, G. *J. Organomet. Chem.* **1989**, *361*, C25.
(20) Aza-[2,3]-Wittig rearrangements are believed to proceed through highly ordered cyclic transition states analogous to those of the corresponding allylic ethers. See refs 10−13.
(21) Wolfe, J. P. In *Comprehensive Organic Synthesis II*, 2nd ed.; Knochel, P., Ed.; Elsevier: Amsterdam, 2014; p 1038.
(22) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624.
(23) Bahy, A.; Kacem, Y.; Hassine, B. B. *Synth. Commun.* **2010**, *40*, 1377.
(24) Kreye, O.; Westermann, B.; Wessjohann, L. A. *Synlett* **2007**, *2007*, 3188.
(25) Meyer, C.; Pete, J.-P.; Piva, O. *Rec. Trav. Chem. Pays-Bays* **1995**, *114*, 492.
(26) Yip, K.-T.; Li, J.-H.; Lee, O.-Y.; Yang, D. *Org. Lett.* **2005**, *7*, 5717.
(27) He, R.; Toy, P. H.; Lam, Y. *Adv. Synth. Catal.* **2008**, *350*, 54.
(28) Zhang, M.; Yang, H.-W.; Zhang, Y.; Zhu, C.-J.; Li, W.; Cheng, Y.-X.; Hu, H.-W. *Chem. Commun.* **2011**, *47*, 6605.
(29) Ou, L.; Shao, J.; Zhang, G.; Yu, Y. *Tetrahedron Lett.* **2011**, *52*, 1430.
(30) Sueki, S.; Kuninobu, Y. *Org. Lett.* **2013**, *15*, 1544.
(31) Reddy, M. M.; Kumar, M. A.; Swamy, P.; Naresh, M.; Srujana, K.; Satyanarayana, L.; Venugopal, A.; Narender, N. *Green Chem.* **2013**, *15*, 3474.
(32) Chang, Y.-H.; Nakajima, Y.; Ozawa, F. *Organometallics* **2013**, *32*, 2210.
(33) Tyagi, V.; Gupta, A. K. *Synth. Commun.* **2014**, *44*, 493.
(34) Tummatorn, J.; Thongsornkleeb, C.; Ruchirawat, S. *Tetrahedron* **2012**, *68*, 4732.
(35) Brucelle, F.; Renaud, P. *J. Org. Chem.* **2013**, *78*, 6245.



DOI: 10.1021/acs.joc.5b01286
*J. Org. Chem.* 2015, 80, 9041−9056

(36) Prasada Rao Lingam, V. S.; Thomas, A.; Mukkanti, K.; Gopalan, B. *Synth. Commun.* **2011**, *41*, 1809.
(37) Ohshima, T.; Miyamoto, Y.; Ipposhi, J.; Nakahara, Y.; Utsunomiya, M.; Mashima, K. *J. Am. Chem. Soc.* **2009**, *131*, 14317.
(38) Sorribes, I.; Junge, K.; Beller, M. *J. Am. Chem. Soc.* **2014**, *136*, 14314.
(39) Kiraly, I.; Hornyanszky, G.; Kupai, K.; Novak, L. *Heterocycles* **2008**, *75*, 43.
(40) Zhang, J.; Jiang, J.; Li, Y.; Zhao, Y.; Wan, X. *Org. Lett.* **2013**, *15*, 3222.
(41) Zhang, J.; Jiang, J.; Li, Y.; Zhao, Y.; Wan, X. *Org. Lett.* **2013**, *15*, 3222.
(42) Stranix, B. R.; Sauve, G.; Bouzide, A.; Cote, A.; Sevigny, G.; Yelle, J. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4289.
(43) McKerrow, J. D.; Al-Rawi, J. M. A.; Brooks, P. *Synth. Commun.* **2010**, *40*, 1161.



DOI: 10.1021/acs.joc.5b01286
*J. Org. Chem.* 2015, 80, 9041−9056