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Article

Tropylium Salt-Promoted Vinylogous Aza-Michael Addition of Carbamates to *para*-Quinone Methides: Elaboration to Diastereomerically Pure α,α'-Diarylmethyl Carbamates

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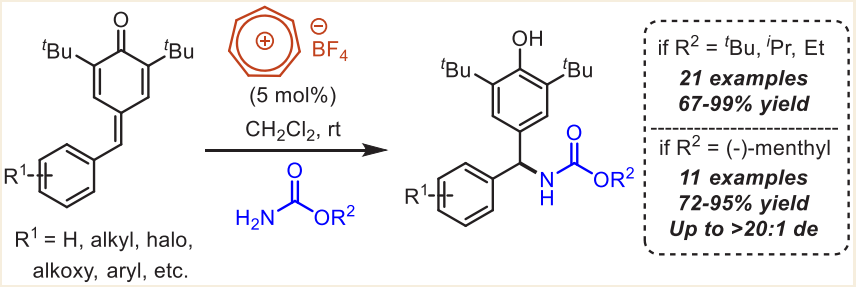

ABSTRACT: Carbocation catalysis is emerging as an important subarea of Lewis acid catalysis. Some stable and isolable carbocations have been successfully utilized as Lewis acid catalysts and promoters in many synthetic transformations. In this manuscript, we report a tropylium cation-promoted vinylogous aza-Michael addition of carbamates to *para*-quinone methides (QMs) to access a wide range of unsymmetrical α,α'-diarylmethyl carbamates. This mild protocol was effective for the vinylogous conjugate addition of (−)-menthyl carbamate to *p*-QMs, and the respective diastereomerically pure α,α'-diarylmethyl carbamate derivatives could be obtained in excellent yields and diastereoselectivities (up to >20:1 de).

KEYWORDS: *Carbocation, Tropylium Salt, Vinylogous Conjugate Addition, para-Quinone Methides, Diarylmethyl Carbamates*

INTRODUCTION

Although stable carbocations such as tritylium and tropylium cations have been known for more than a century, their synthetic applications, especially in organic transformations, have been uncovered only recently. Particularly, the tritylium carbocation has been successfully employed as a Lewis acid promoter or catalyst in numerous fundamental organic transformations.[1,2] The unique Lewis acidic character of the tritylium carbocation originates from the low-lying vacant p_c orbital, which can activate the electrophile (typically carbonyl group) by accepting electrons and tune the electrophile toward nucleophilic attack.[3] However, although the tropylium carbocation was first isolated in 1891,[4] the utility of this cation as a reagent or a mediator or catalyst in synthetic organic chemistry has only been realized over the last couple of decades.[5] For example, Lambert and co-workers demonstrated the utility of the tropylium cation as a mediator in the α-cyanation of amines with KCN.[6] Later, Nguyen's group demonstrated the catalytic utility of the tropylium cation (mostly as a Lewis acid) in several synthetic methodologies, such as acetalization and *trans*-acetalization reactions,[7] carbonyl−olefin metathesis reactions,[8] retro-Claisen-type reactions,[9] O−H insertion reactions of carboxylic acids with diazo compounds,[10] etc.[11−16] In this manuscript, we intend to demonstrate the catalytic utility of tropylium salts in the vinylogous aza-Michael reactions of *para*-quinone methides (*p*-QMs)[17−20] to access unsymmetrical α,α'-diarylmethyl amine derivatives. These compounds have been well-recognized in the area of medicinal chemistry, and many α,α'-diarylmethyl amine-based drugs have been already commercialized (Figure 1).[21,22] Numerous synthetic methods have been established to access α,α'-diarylmethyl amine or carbamate derivatives,[23] including the arylation of imines,[24−29] the amination of diarylmethanols,[30−37] benzylic C−H amination via cross-dehydrogenative coupling,[38,39] the Lossen rearrangement of hydroxamic acids,[40,41] the reduction and transfer hydrogenation of imines,[42−50] the direct reductive amination of ketones,[51−55] the aryl migration of azides,[56] desulfonylative amination,[57] etc. A few other protocols have also been reported for the preparation of diarylmethyl amines from *p*-

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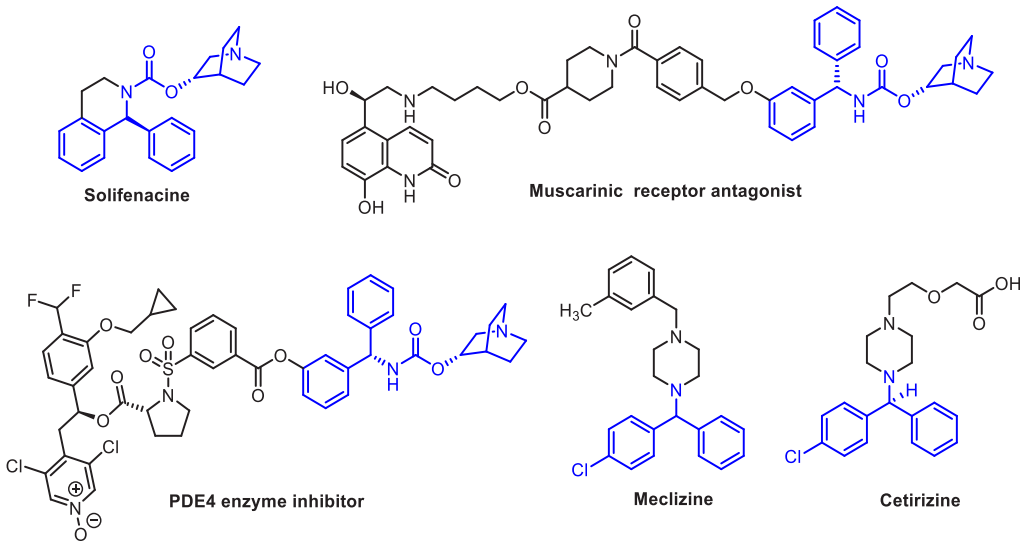


Figure 1. Some of the α,α'-diarylmethyl amine- or carbamate-based drugs.

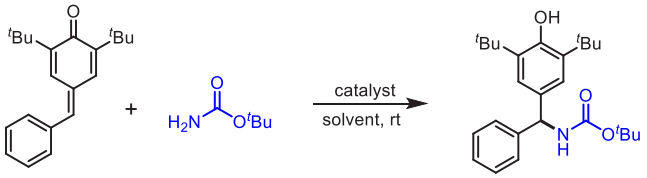
QMs through the base- or Lewis acid-mediated or catalyzed vinylogous conjugate addition of amines and amides.[58−61]

Recently, our research group has explored the inimitable reactivity of *p*-QMs to access unsymmetrical diaryl- and triarylmethane derivatives, carbocycles, and heterocycles.[62−67] While working in this area,[20] we realized that the concept of "carbocation catalysis" has not yet been utilized in vinylogous conjugate addition reactions of *p*-QMs, although this concept has been well explored in the activation of simple aldehydes.[7−16] Therefore, we decided to employ a tropylium salt as a catalyst or promoter for the vinylogous aza-Michael addition of carbamates to *p*-QMs to obtain α,α'-diarylmethyl carbamate derivatives. We envisioned that the tropylium salt could activate the *p*-QM, thereby making it more susceptible for nucleophilic attack with the carbamate. In fact, when we started this work, our objective was to prepare a diastereomerically pure α,α'-diarylmethyl carbamate through an auxiliary-controlled diastereoselective addition of chiral carbamates to *p*-QMs. However, before developing the diastereoselective version, we decided to develop this methodology with simple alkyl carbamates to portray the generality and scope of this transformation.

RESULTS AND DISCUSSION

To find the optimal conditions, many experiments were performed under various conditions using a *p*-QM **1a**, *tert*-butyl carbamate (**2a**), and tropylium tetrafluoroborate (as a catalyst), and the outcomes are depicted in Table 1. The very first experiment itself using 2.5 mol % tropylium tetrafluoroborate in MeCN worked efficiently, and the expected α,α'-diarylmethyl carbamate **3a** was isolated in a 90% yield (entry 1). The reaction was also performed in other solvents such as THF and Et_2O. However, in the case of THF, the reaction did not reach completion even after 48 h although the product **3a** was formed in a good yield (entry 2). Unfortunately, in the case of the reaction in Et_2O, no product formation was observed even after 24 h (entry 3). Other solvents such as toluene and CH_2Cl_2 were also found to be appropriate as in those cases **3a** was isolated in 75 and 90% yields, respectively (entries 4 and 5, respectively). The yield of the product was enhanced considerably (to 96%) when the concentration of the catalyst was increased to 5 mol % (entry 6). The product

Table 1. Catalyst Screening and Optimization Study[a]



1a (1.0 equiv.) **2a** (1.2 equiv.) **3a**

entry	catalyst	catalyst (mol %)	solvent	time (h)	yield (%)[b]
1	$Trop^+BF_4^-$	2.5	MeCN	1.0	90
2	$Trop^+BF_4^-$	2.5	THF	48	85
3	$Trop^+BF_4^-$	2.5	Et_2O	24	0
4	$Trop^+BF_4^-$	2.5	PhMe	48	75
5	$Trop^+BF_4^-$	2.5	CH_2Cl_2	1.0	90
6	**$Trop^+BF_4^-$**	**5.0**	**CH_2Cl_2**	**1.0**	**96**
7	$Trop^+ClO_4^-$	5.0	CH_2Cl_2	1	94
8[c]	$Bi(OTf)_3$	5.0	CH_2Cl_2	5	84
9[c]	$Ce(OTf)_3$	5.0	CH_2Cl_2	15	82
10	AgOTf	5.0	CH_2Cl_2	12	70
11	$Cu(OTf)_2$	5.0	CH_2Cl_2	12	70
12	$Sc(OTf)_3$	5.0	CH_2Cl_2	24	42
13	$Yb(OTf)_3$	5.0	CH_2Cl_2	24	24
14	$B(C_6F_5)_3$	5.0	CH_2Cl_2	20	96
15	$Ph_3C^+BF_4^-$	5.0	CH_2Cl_2	1	94
16	--	--	CH_2Cl_2	24	0
17	$Et_4N^+BF_4^-$	5.0	CH_3CN	24	25

[a]All reactions were performed using **1a** (0.170 mmol) and **2a** (0.204 mmol) in 1.5 mL of solvent. [b]Isolated yields. [c]Time (min).

3a was obtained in a 94% yield in an hour when tropylium perchlorate was used instead of tropylium tetrafluoroborate (entry 7). To compare the catalytic efficiency of tropylium with those of other Lewis acids in this transformation, a few additional experiments were carried out using metal triflates (entries 8−13). However, in all those cases the yield of **3a** was much lower when compared to that in the tropylium salt-catalyzed reaction. In contrast to other metal catalysts, the boron-based Lewis acid $B(C_6F_5)_3$ was found effectively catalyze this transformation (entry 14). However, in this case, the reaction took a very long time to reach completion.

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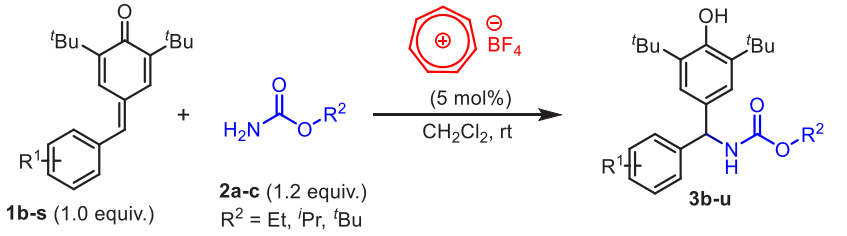
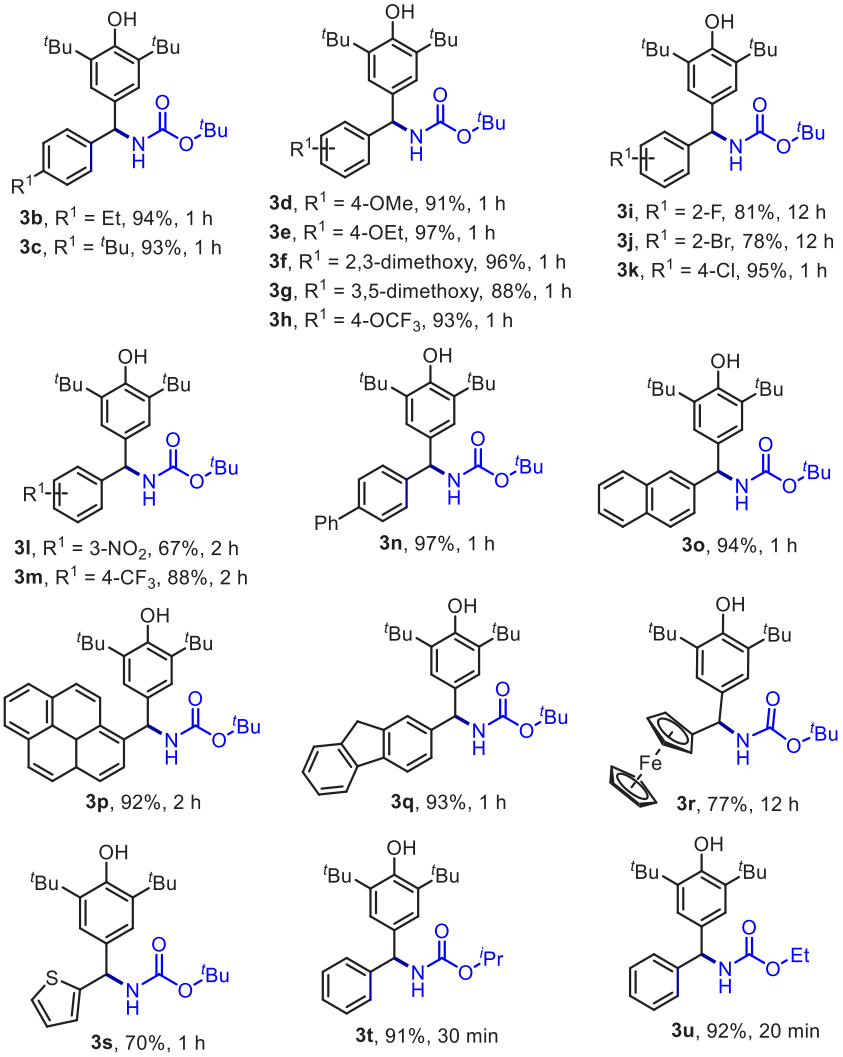
Chart 1. Substrate Scope with Various *p*-QMs and Carbamates[a]





[a]All reactions were done on a 50 mg scale of **1b−s** in 1.5 mL of CH_2Cl_2. Yields correspond to isolated yields.

Interestingly, the much-explored organic Lewis acid tritylium tetrafluoroborate was equally effective for this reaction (when compared to the tropylium catalyst), as **3a** was obtained in a 94% yield within an hour (entry 15). There was no reaction without the catalyst, which means a catalyst is required to drive this reaction (entry 16). In addition, since BF_4^- is the counteranion in the tropylium salt that was used in the optimization studies, an additional experiment was carried out with 5 mol % of Et_4NBF_4 (entry 17). In that case, the product was obtained in only a 25% yield after 24 h.

Since "tropylium catalysis" has not been explored much in Lewis acid-catalyzed transformations, we utilized tropylium salt as a catalyst for substrate scope studies. The optimized reaction conditions (entry 6, Table 1) were employed to investigate the substrate scope and limitations using various *p*-QMs and carbamates, and the results are shown in Chart 1. The reactions of *t*-butyl carbamate with *p*-QMs (**1b−h**) worked really well, and the corresponding *α*,*α*′-diarylmethyl carbamates **3b−h** were produced in 88−97% yields. Other precursors (**1i−k**), which were substituted with halo-substituted arenes, also gave the desired products **3i−k** in 78−95% yields. In the cases of *p*-QMs **1l** and **1m**, where the *p*-QM was substituted with electron-poor arenes, the desired products **3l** and **3m** were isolated in 67% and 88% yields, respectively. Other *p*-QMs (**1n−q**), which were derived from aromatic aldehydes substituted or fused with aryl or alicyclic rings, underwent a smooth reaction with *t*-butyl carbamate to give the respective compounds **3n−q** in >90% yields. The

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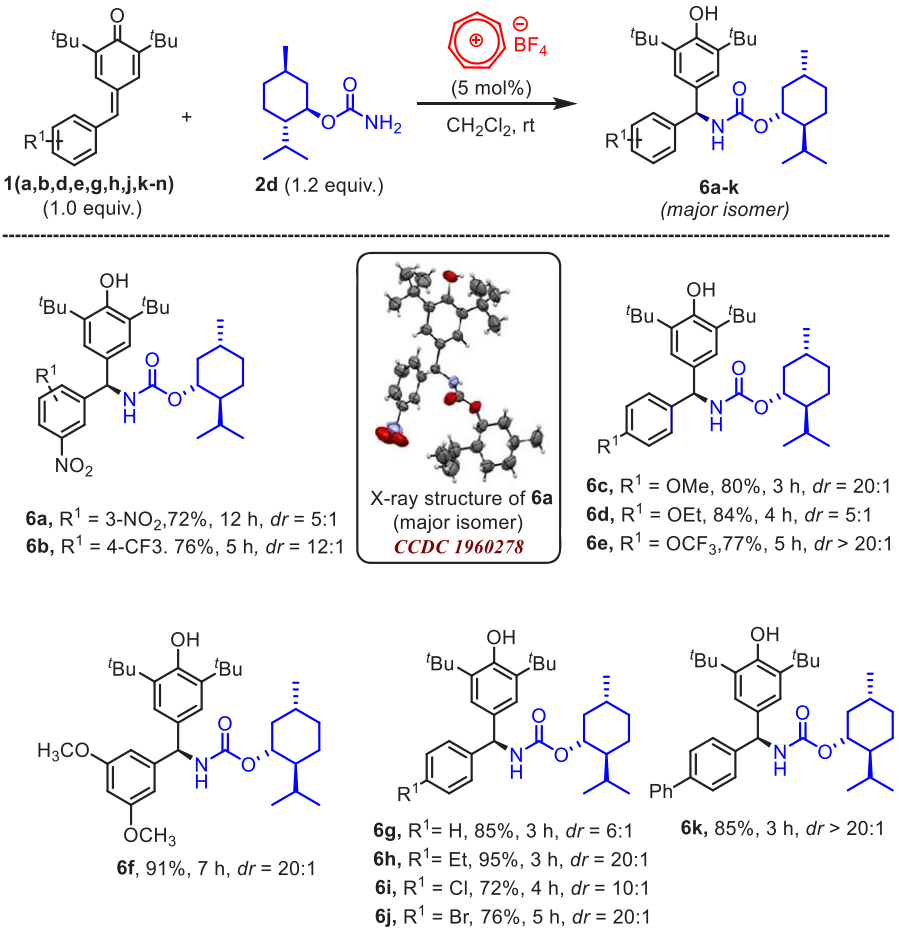
Chart 2. Substrate Scope with Various *p*-QMs and (−)-Menthyl Carbamate[a]



[a]All reactions were performed on a 50 mg scale of **1a**, **1b**, **1d**, **1e**, **1g**, **1h**, **1j**, or **1k**−**n** in 1.5 mL of CH_2Cl_2. Yields reported here are combined isolated yields of both the isomers. dr's were assigned from ^1H NMR analysis of the crude mixtures.

α,*α*′-diarylmethyl carbamates **3r** and **3s** were isolated in 77% and 70% yields when we used ferrocene- and thiophene-based *p*-QMs **1r** and **1s**, respectively. Other carbamates such as isopropyl and ethyl carbamates provided the respective products **3t** and **3u** in 91% and 92% yields, respectively, within half an hour under optimal conditions.

As mentioned earlier, our objective was to synthesize diastereomerically pure *α*,*α*′-diarylmethyl carbamates, which can be elaborated to some useful optically pure drug molecules. Since (−)-menthyl carbamate was easily accessible, we decided to evaluate the vinylogous aza-Michael addition of (−)-menthyl carbamate to *p*-QMs. Chart 2 shows the summary of the reaction between (−)-menthyl carbamate and various *p*-QMs under optimized conditions. It is evident from Chart 2 that most of the *p*-QMs reacted with (−)-menthyl carbamate (**2d**) in the presence of 5 mol % tropylium tetrafluoroborate in CH_2Cl_2. In the case of the 3-nitro-phenyl-substituted *p*-QM (**1l**), a diastereomeric mixture (5:1 dr) of **6a** was obtained in a 72% yield. Fortunately, we were able to separate the diastereomers by column chromatography and crystallize the major isomer of **6a**. The structure of the major isomer of **6a** was confirmed by single-crystal X-ray analysis (CCDC 1960278). Other diastereomerically pure carbamate derivatives (**6b**−**k**) could be obtained in 72−95% yields and 5:1 to >20:1 dr's. The absolute stereochemistry of the other carbamates **6b**−**k** was assigned based on the X-ray structure of the major isomer of **6a**. In most of the cases, the dr's of the respective products (**6c**, **6e**, **6f**, **6h**, **6j**, and **6k**) were found to be >20:1.

Since we demonstrated the catalytic utility of tropylium salt in the vinylogous conjugate reactions of *p*-QMs, we were curious to investigate the exact role of the tropylium cation in this particular reaction. Since carbonyl activation by a tropylium cation has been well studied,[7−16] we were partly convinced that the tropylium cation activated the C═O group of the *p*-QM (**1a**), followed by the subsequent addition of the carbamate (**2a**) to the activated *p*-QM in a 1,6-fashion to give the product **3a**. But still have decided to perform a few control experiments to determine the exact mode(s) of activation. We believed that if the C═O of *p*-QM was activated by tropylium cation, there would be a shift in the signal of C═O carbon of the *p*-QM in the NMR spectra (^{13}C NMR) when titrated with different concentrations of tropylium salt. Therefore, the ^{13}C NMR spectra for the mixture of **1a** and tropylium tetrafluoroborate at various molar ratios were recorded in CD_3CN and stacked. As expected, the chemical shift of the carbonyl carbon of **1a** (187.2621 ppm) gradually and slightly shifted toward the upfield region (187.0005 ppm with 10 equiv of tropylium salt with respect to **1a**) with the increasing concentration of tropylium tetrafluoroborate. Since the shift is not significant (difference of 0.26 ppm), it is not very clear whether the carbonyl group of **1a** gets activated by the

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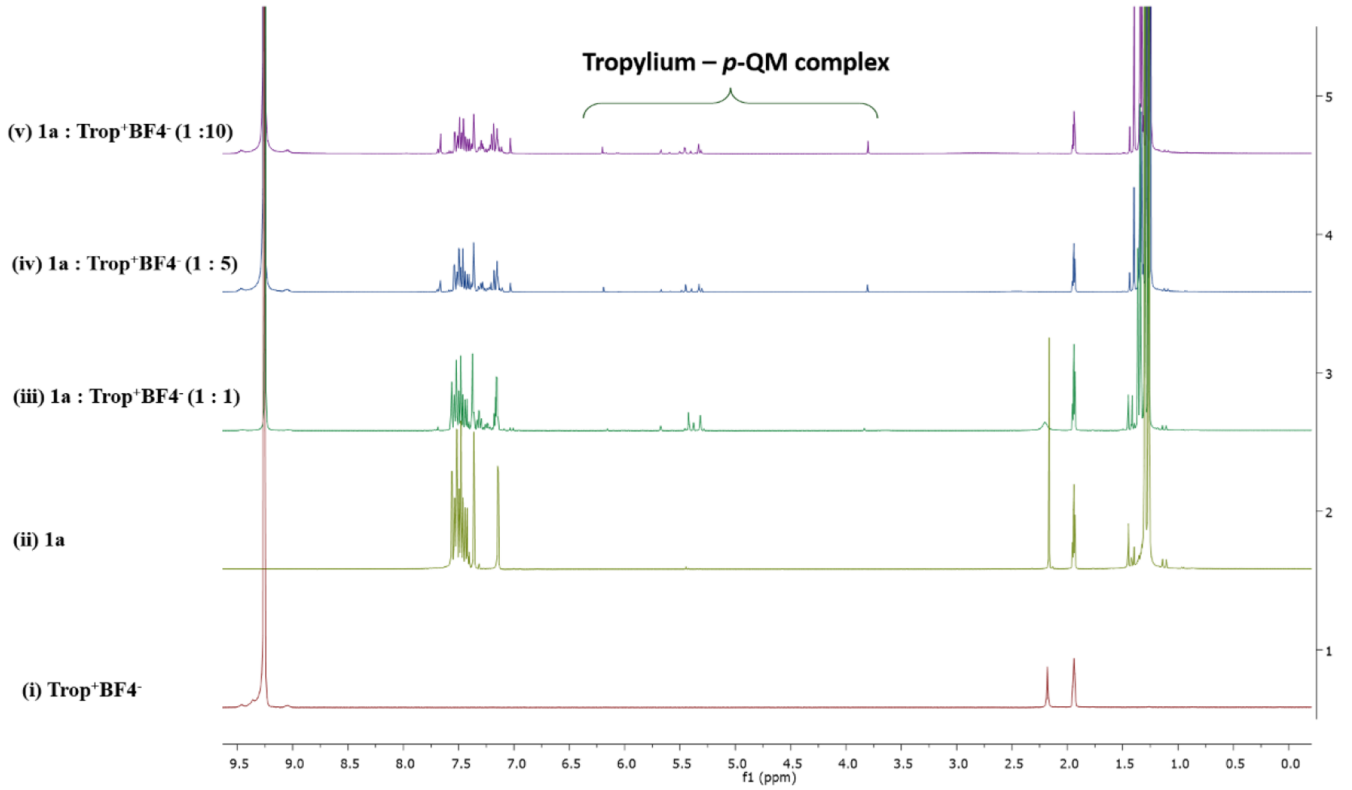
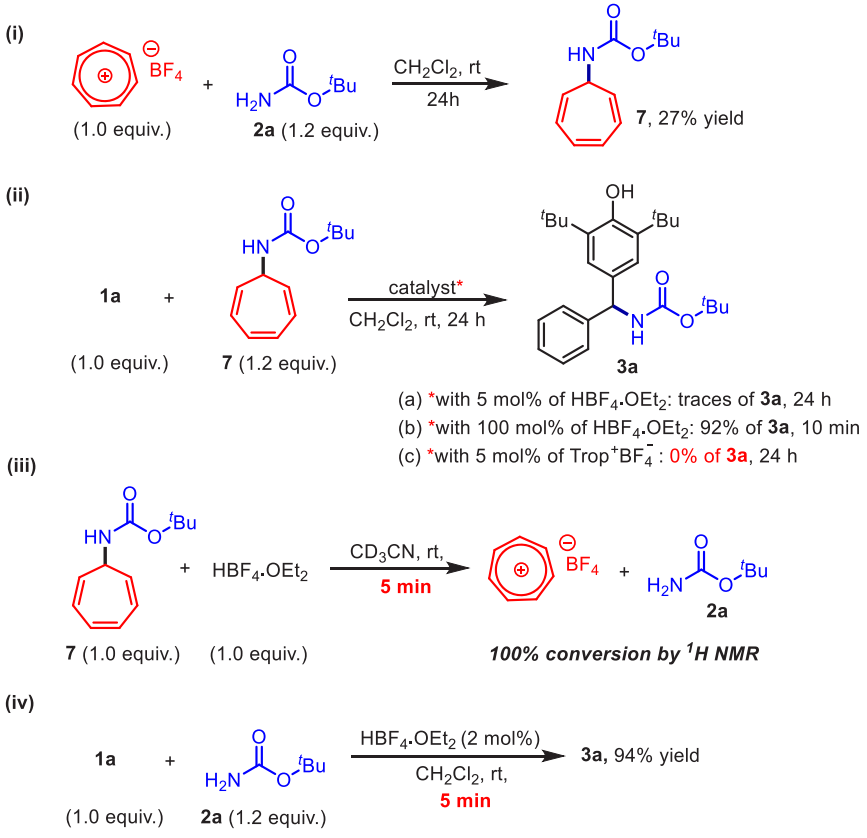


Figure 2. ^{1}H NMR control experiments with **1a** and tropylium tetrafluoroborate in CD_3CN. The stoichiometric ratios between *p*-QM (**1a**) and tropylium tetrafluoroborate and the chemical shifts of the protons of the Trop$^+$BF$_4^-$–*p*-QM complex in the ^{1}H NMR spectra are indicated. Shifts are relative to tetramethylsilane (TMS). The concentration of **1a** was 102 mM.

Scheme 1. Control Experiments



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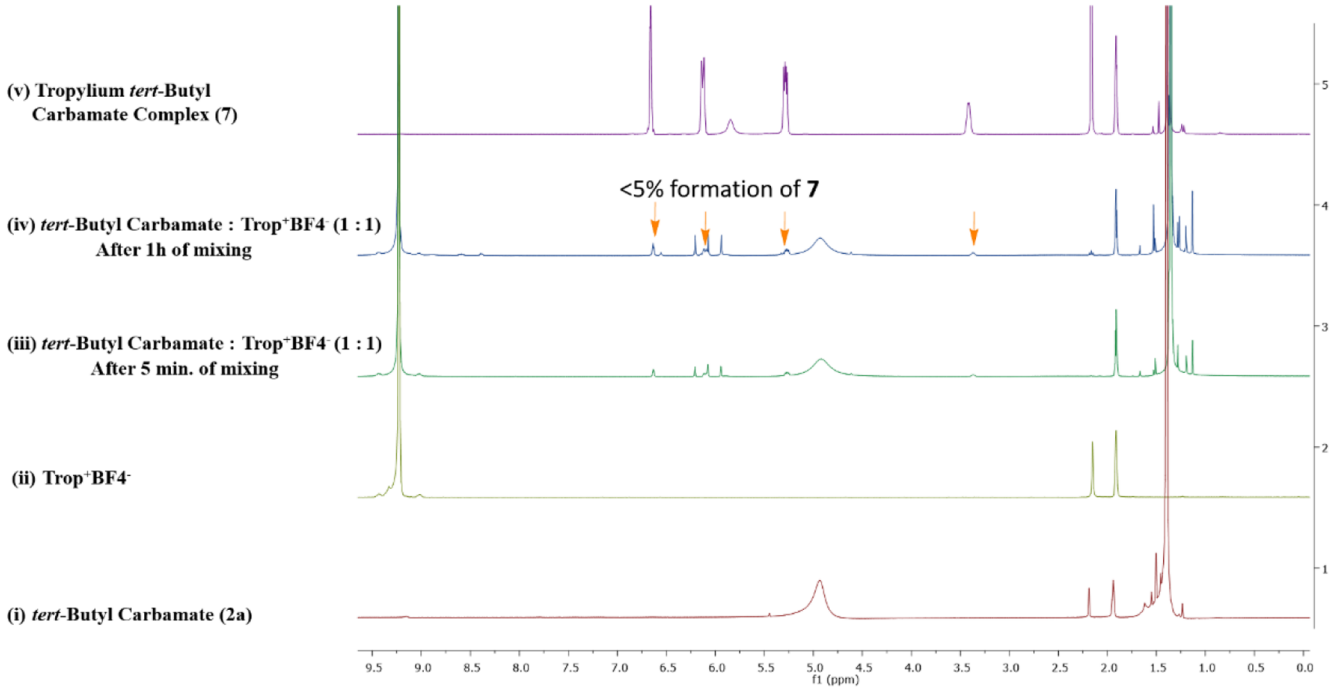

Figure 3. Stacked ^{1}H NMR spectra of pure **2a**, pure Trop$^+$BF$_4^-$, a 1:1 mixture of **2a** and Trop$^+$BF$_4^-$, and pure **7**.

tropylium salt. However, interestingly, when the titration experiment between **1a** and tropylium tetrafluoroborate at various molar ratios was monitored by ^{1}H NMR spectroscopy, a few new signals appeared in the aliphatic region (3.5−6.5 ppm) when the amount of tropylium salt was increased progressively with respect to **1a** (Figure 2). A similar kind of observation was reported by Nguyen and co-workers for the activation of cyclic ketones by the tropylium cation.[10] Moreover, in our case, there were a few more new signals that appeared in the aromatic region (7.0 to 7.8 ppm) as well. These observations clearly indicate that there is some kind of interaction between the tropylium cation and **1a**, although the exact mode of complexation or activation is unclear.

Another possibility is the activation of the nucleophile (carbamate in this case) by the tropylium cation. It is known in the literature that tropylium cation can react with electron-rich molecules such as anilines or indoles to form the corresponding adducts.[68] Therefore, to understand whether this mode of activation (between carbamate and the tropylium cation) was operating in our protocol, we performed a reaction between tropylium tetrafluoroborate and *t*-butyl carbamate (**2a**). In that case, the adduct **7** was isolated in a 27% yield (i, Scheme 1). Therefore, it is possible that the adduct **7** could be an intermediate in the reaction. In addition, the reaction between **2a** and tropylium tetrafluoroborate would potentially lead to the formation of HBF_4, which could act as a catalyst for the vinylogous conjugate addition of **7** to **1a** to generate the product **3a**. However, when the adduct **7** was subjected to a vinylogous conjugate addition reaction with **1a** using 5 mol % $HBF_4{\cdot}OEt_2$, only traces of **3a** were observed (ii (**a**), Scheme 1). Interestingly, the reaction between **7** and **1a** with stoichiometric quantities of $HBF_4{\cdot}OEt_2$ generated **3a** in a 92% yield within 10 min (ii (**b**), Scheme 1). However, the analysis of the crude reaction mixture by ^{1}H NMR spectroscopy revealed signals that corresponded to *t*-butyl carbamate (**2a**) in addition to those for the product **3a** and tropylium tetrafluoroborate. Since adduct **7** was employed in slight excess (1.2 equiv) (ii (**b**), Scheme 1) in this reaction with respect to **1a**, we expected signals that corresponded to unreacted **7** (at least 0.2 equiv) in the ^{1}H NMR spectrum of the crude. However, no signals that corresponded to the adduct **7** were observed in the crude ^{1}H NMR spectrum. Hence, possibly, the adduct **7** gets decomposed into **2a** and tropylium tetrafluoroborate in the presence of $HBF_4{\cdot}OEt_2$. Moreover, this observation also indicates that the formation **7** could be reversible under the reaction conditions. To confirm this, equimolar quantities of $HBF_4{\cdot}OEt_2$ and **7** were mixed in CD_3CN (in NMR tube), and the reaction progress was observed by NMR spectroscopy. As expected, **7** was completely converted to tropylium tetrafluoroborate and *t*-butyl carbamate (**2a**) in quantitative yields (as determined by ^{1}H NMR analysis) within 5 min (iii, Scheme 1). Therefore, it is evident from this experiment that the formation of **7** is indeed reversible. This result also explains why the reaction between the adduct **7** and **1a** worked well with the stoichiometric quantities of $HBF_4{\cdot}OEt_2$ (ii (**b**), Scheme 1). In this case, we believe that $HBF_4{\cdot}OEt_2$ converts the adduct **7** to *t*-butyl carbamate (**2a**) and tropylium tertrafluoroborate and **2a** subsequently experiences vinylogous aza-Michael addition with **1a** to give the product **3a**. In another control experiment, the adduct **7** was treated with **1a** in the presence of 5 mol % tropylium tetrafluoroborate, and the product **3a** was not detected at all even after 24 h (ii (**c**), Scheme 1). Based on these observations, one can confirm that the reaction does not proceed through the vinylogous conjugate addition of the adduct **7** to *p*-QM (**1a**).

Another possibility arises here. The HBF_4 formed in situ during the reaction between **2a** and tropylium tetrafluoroborate could probably also act as a catalyst in the 1,6-addition reaction of **2a** with **1a**. To understand this, a reaction was performed between **1a** and **2a** in the presence of 2 mol % $HBF_4{\cdot}OEt_2$, and **3a** was obtained in a 94% yield within 5 min

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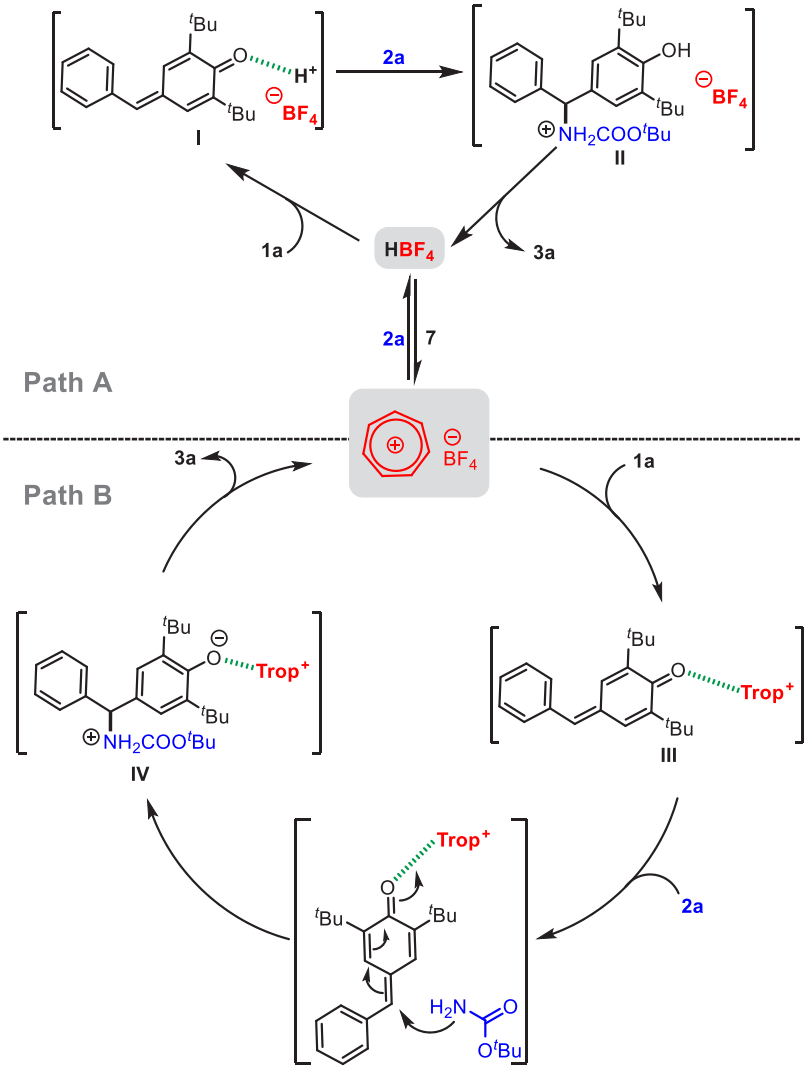
Scheme 2. Plausible Reaction Mechanism



(iv, Scheme 1). Consequently, one cannot exclude the involvement of in situ generated HBF_4 in catalyzing this transformation. However, when equimolar quantities of **2a** and tropylium tetrafluoroborate were mixed (in CD_3CN and monitored by ^1H NMR spectroscopy), less than a 5% yield of the adduct **7** was observed in the ^1H NMR spectrum (Figure 3). In reality, however, only 5 mol % tropylium salt was found to be sufficient to catalyze the reaction (entry 6, Table 1). This means that very minute quantities of HBF_4 are generated in situ in the reaction mixture. Therefore, the possibility here is that, the reaction probably takes a relatively long time for completion since the concentration of HBF_4 is much lower in the reaction mixture as it is also involved in the decomposition of the tropylium−carbamate complex (**7**).

Based on the outcomes from the control experiments, two possible mechanisms have been proposed (Scheme 2). The first proposal (path A) is based on hidden Brønsted acid catalysis. Initially, the carbamate **2a** reacts with tropylium salt and generates the tropylium-carbamate complex **7** along with HBF_4, which is involved in the activation the *p*-QM (**1a**) through H-bonding. Subsequently, the 1,6-conjugate addition of carbamate (**2a**) takes place to generate an intermediate **II**, which finally decomposes to the product **3a**. During this process, HBF_4 gets regenerated (path A). Another alternative possibility (Path B) is the involvement of tropylium carbocation in the activation of *p*-QM (**1a**). Since the ^1H NMR titration experiment between **1a** and tropylium salt revealed that there is an interaction between **1a** and the tropylium cation (Figure 2), one cannot rule out the possibility of tropylium catalysis. Therefore, another possibility (path B) is that the tropylium cation initially complexes with *p*-QM (**1a**) through a weak interaction, which leads to the formation of activated complex **III**. Next, the *t*-butyl carbamate (**2a**) adds to the complex **III** to form **IV**, which further undergoes proton exchange to give the product **3a** with the expulsion of tropylium salt (catalyst).

Next, we shifted our attention to elaborate the established protocol to some useful compounds. We envisioned that the hydrolysis of **6i** would lead to an enantiomerically pure diaryl amine (*S*)-**8**. (*S*)-**8** is a common intermediate for (*S*)-cetirizine dihydrocholoride (Figure 1),[69] which is widely used for the treatment of allergies. In this regard, the hydrolysis of **6i** was carried out under various acidic and basic conditions (dilute HCl, TfOH, TFA, and KOH) [Scheme 3]. However, the retro-1,6-addition unfortunately took place under all these conditions and, as a result, only the *p*-QM **1a** was observed. The expected derivative (*S*)-**8** was not observed under any of those conditions. Similar results were obtained when we

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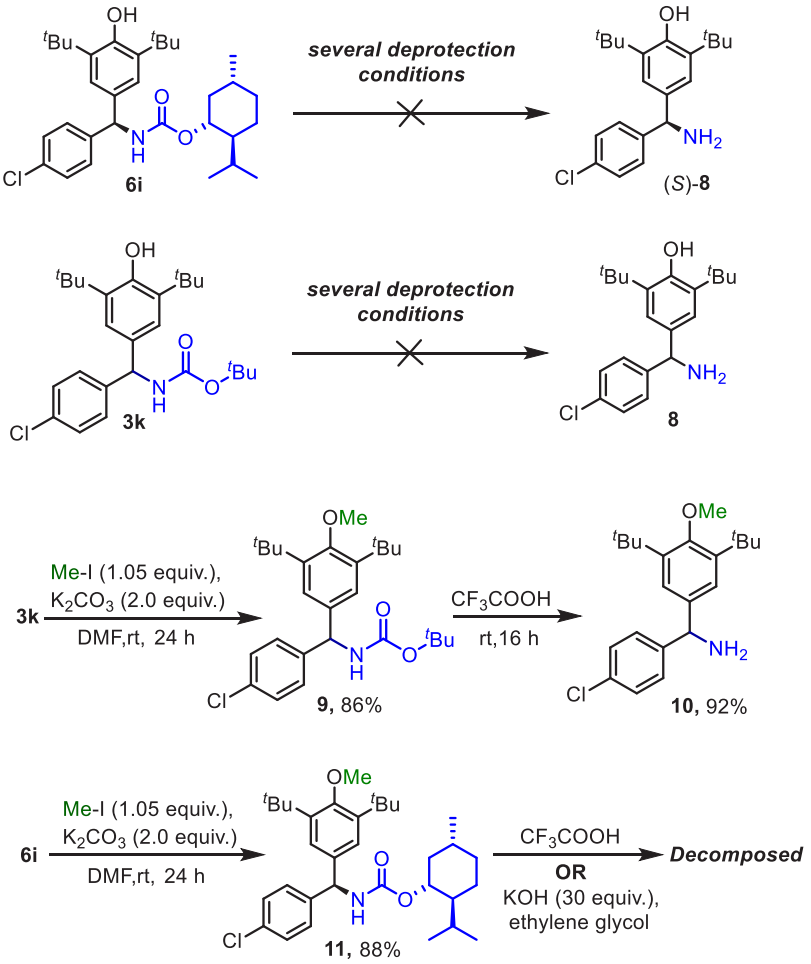
Scheme 3. Synthetic Elaborations of α,α'-Diarylmethyl Carbamates 6i and 3k



carried out the hydrolysis reaction of **3k** under acidic or basic conditions. In fact, the formation of **1a** can be explained as follows. We think, most likely, that hydrolysis takes place in both the cases (**6i** and **3k**) under acidic conditions to give the diaryl amine **8** or (*S*)-**8**. However, under acidic conditions the amine group of **8** or (*S*)-**8** is probably protonated and becomes ammonium salt, which indeed is a very good leaving group. Therefore, under acidic conditions **8** or (*S*)-**8** gets converted to **1a** with the expulsion of ammonia. Under basic conditions, the base probably abstracts the phenolic proton of **6i** or **3k**, which finally leads to the elimination of the whole carbamate group (good leaving group) from **6i** or **3k** to generate **1a**. At this point, we thought that protecting the phenolic group as a methoxy group in **3k** and **6i** would help arrest the retro-1,6-addition reaction. Subsequently, the selective *O*-methylation reaction of **3k** and **6i** was performed under basic conditions using a reported procedure,[70] and the desired methylated compounds **9** and **11** were obtained in 86% and 88% yields, respectively. Gratifyingly, the hydrolysis of **9** worked efficiently with trifluoroacetic acid[71] to give the desired diaryl amine **10** in a 92% yield under mild conditions (Scheme 3). Similarly, the hydrolysis of **11** was carried out under acidic (CF_3COOH) and basic (KOH)[72] conditions. Unfortunately, however, both the reactions end with the decomposition of **11**.

CONCLUSIONS

In this article, we have disclosed an operationally simple protocol for the synthesis of α,α'-diarylmethyl carbamates in satisfactory yields through a tropylium salt-promoted vinylogous aza-Michael addition of a variety of alkyl carbamates to *p*-quinone methides (*p*-QMs). This methodology was also employed to prepare diastereomerically pure α,α'-diarylmethyl carbamates (dr's up to >20:1) via an auxiliary-controlled vinylogous conjugate addition of (−)-menthyl carbamates to *p*-QMs. Since the diarylmethyl amine or carbamate core is found as an integral unit in many unnatural and pharmaceutically active drug molecules, we are certain that this protocol would definitely useful in the synthesis of those drug molecules and related analogues.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsorginorgau.1c00033.

All experimental details, including chemical procedures and characterization data of all products, and copies if ^1H, ^{13}C, and ^{19}F NMR spectra (PDF)

Accession Codes

CCDC 1960278 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing

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Notes

The authors declare no competing financial interest.

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