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Organocatalytic Enantioselective 1,8-Addition for the Synthesis of Chiral Tetraarylmethanes from 2-Naphthol/Naphthalen-2-amine-Based Tertiary Alcohols

Meiwen Liu,[‡] Boming Shen,[‡] Chang Liu, Peiyuan Yu,* and Pengfei Li*

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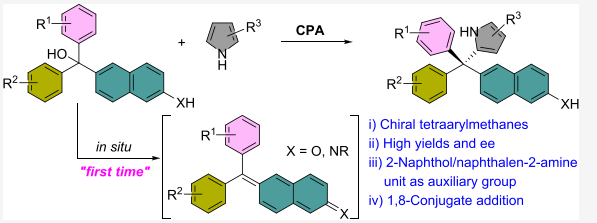
ABSTRACT: Catalytic enantioselective construction of optically active tetraarylmethanes remains a challenging issue in the field of asymmetric synthesis because of the overwhelming steric hindrance and formidable stereocontrol that existed in construction of the all-aryl-substituted quaternary carbon stereocenter. Here, we reported an organocatalytic asymmetric synthesis of chiral tetraarylmethanes from racemic tertiary alcohols. With the aid of a chiral phosphoric acid catalyst, 6-methylenenaphthalen-2(6*H*)-ones were generated in situ from 6-(hydroxydiarylmethyl)naphthalen-2-ols, followed by stereoselective 1,8-conjugate addition to afford the corresponding tetraarylmethanes in high to excellent yields with high enantioselectivities. Furthermore, the scope of tertiary alcohols has been successfully enlarged to 6-(hydroxydiphenylmethyl)naphthalen-2-amines. Notably, it is the first time to use 2-naphthol/naphthalen-2-amine unit as the auxiliary group to in situ generate *α,β,γ,δ,ε,ζ*-conjugate systems, which have been successfully involved in organocatalytic remote stereocontrolled 1,8-conjugate addition reactions. Particularly, organocatalytic stereoconvergent formal nucleophilic substitution reaction of triarylmethanols has been achieved for the asymmetric construction of chiral tetraarylmethanes. In addition, DFT calculations have been applied to provide guidance for the design of additional tertiary alcohols and understand the origin of stereoselectivity.



INTRODUCTION

Catalytic enantioselective construction of tetrasubstituted carbon stereocenters plays an essential role in the field of modern asymmetric synthesis.[1] Benefiting from its unique structure and related reactivity, asymmetric nucleophilic substitution reaction of tertiary alcohols would provide direct access to tetrasubstituted carbon stereocenters, which is fascinating but full of daunting challenges in terms of steric effects and asymmetric induction. Particularly, catalytic asymmetric synthesis of enantioenriched tetraarylmethanes from racemic triarylmethanols is very rare.[2] To fill this gap, we were motivated to develop an organocatalytic enantioselective reaction of tertiary alcohols for the asymmetric synthesis of chiral tetraarylmethanes.

In general, the nucleophilic substitution reaction of tertiary alcohols goes through the S_N1 mechanism (Scheme 1A). The dehydration to form tertiary carbocation is the rate-limiting step, and the nucleophilic attack to tertiary carbocation would act as the stereoselectivity-determining step in the asymmetric process. Accordingly, a suitable auxiliary group would be essential to stabilizing tertiary carbocation and guiding the nucleophilic attack with the aid of a chiral catalyst, furnishing the desired results. Notably, several types of auxiliary groups have been developed, enabling the corresponding alcohols to be successfully involved in organocatalytic enantioselective reactions. As shown in Scheme 1B,C, these functionalized alcohols dehydrated under acidic conditions to in situ generate *o*-quinone methides (*o*-QMs),[3] aza-*o*-quinone methides (aza-*o*-QMs),[4] *p*-quinone methides (*p*-QMs),[5] aza-*p*-quinone methides (aza-*p*-QMs),[6] 7-methyleneindoles,[7] 3-methyleneindoles,[8] 2-methyleneindoles,[9] and 6-methyleneindoles,[7b,10] followed by conjugate addition to complete the formal enantioselective nucleophilic substitution reactions. Particularly, a breakthrough in the field of organocatalytic construction of chiral tetraarylmethanes from tertiary alcohols was made by Sun and co-workers.[11] With suitable *p*-QMs/2-methyleneindoles formed in situ from racemic triarylmethanols, they graciously realized that a chiral phosphoric acid catalyzed a stereoconvergent formal nucleophilic substitution reaction.

Notably, two major challenges should be considered in the field of organocatalytic enantioselective construction of chiral tetraarylmethanes from racemic triarylmethanols: (1) the introduction of the auxiliary group should favor dehydration of alcohols and stabilize tertiary carbocations; (2) the

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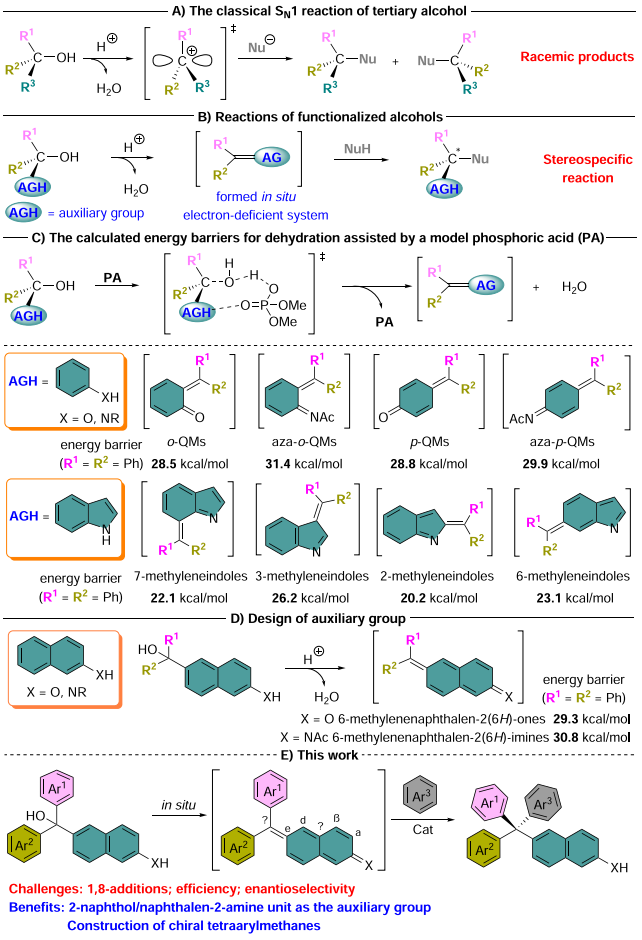
Scheme 1. Reactions of Tertiary Alcohols and Reaction Design



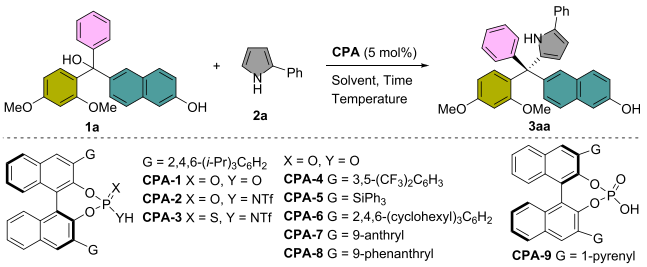
stereodifferentiation among the auxiliary group and other aromatic groups as well as the suitable catalytic system could dominate stereoselectivity. To shed light on the development of the new type of auxiliary group, we calculated the corresponding energy barriers for the dehydration of reported functionalized alcohols assisted by a model phosphoric acid (**PA**) using density functional theory (DFT). As shown in Scheme 1C, using either hydroxyphenyl or aminophenyl as an auxiliary group, the energy barriers of dehydration fluctuate in the range of 28.5 to 31.4 kcal/mol. The energy barriers of dehydration fluctuate in the range of 20.2 to 26.2 kcal/mol when indolyl is employed as an auxiliary group. Given that naphthalene is generally more reactive than benzene, we chose either 2-naphthol or naphthalen-2-amine as the auxiliary group (Scheme 1D). Encouragingly, DFT calculations indicated that the energy barrier of dehydration of 6-(hydroxydiphenylmethyl)naphthalen-2-ol to generate 6-methylenenaphthalen-2(6*H*)-one is 29.3 kcal/mol and the energy barrier of dehydration of *N*-acetyl-6-(hydroxydiphenylmethyl)-naphthalen-2-amine to form 6-methylenenaphthalen-2(6*H*)-imine is 30.8 kcal/mol, which indicates that these units might be good auxiliary groups, enabling the corresponding tertiary alcohols to smoothly undergo unimolecular nucleophilic substitution reaction. In terms of stereoselectivity, different aromatic groups would be inserted into the framework of triarylmethanols. In addition, suitable reaction partners and catalytic systems are also key elements to successful stereocontrol. Fully aware of the difficulties but also of the potential benefits, as part of our ongoing interest in the field of organocatalytic asymmetric reactions of the functionalized alcohols,[6b,e,7c,10] we decided to develop an organocatalytic enantioselective synthesis of chiral tetraarylmethanes from racemic triarylmethanols (Scheme 1E).

RESULTS AND DISCUSSION

Initially, we employed triarylmethanol **1a** and 2-phenyl-1*H*-pyrrole **2a** as model substrates to optimize reaction conditions (Table 1). After careful screening of chiral phosphoric acids (CPAs),[12] it was confirmed by the results that the 2-naphthol unit could play the role of the auxiliary group (Table 1, entries 2−9). In particular, the **CPA-9**-mediated reaction afforded the desired product **3aa** in 82% yield with 72% ee (Table 1, entry 9). Encouragingly, after further modifying reaction parameters including reaction media (Table 1, entries 10−13), temperature (Table 1, entries 14−19), and catalyst loading (Table 1, entry 19), the optimal condition was identified as the following protocol: when **1a** (0.05 mmol) was treated with **2a** (0.06 mmol) in the presence of **CPA-9** (10 mol %) in CH_2Cl_2 (0.5 mL) at −40 °C for 48 h, the desired tetraarylmethane **3aa** was isolated in 92% yield with 92% ee (Table 1, entry 18).

With the optimized conditions in hand, we examined the scope of the **CPA-9** catalyzed reaction of functionalized tertiary alcohols **1** with aromatic nucleophiles **2**. As shown in

Table 1. Optimization of Conditions[a]



entry	CPA	solvent/t, °C/t (h)	yield (%)[b]	ee (%)[c]
1	**CPA-1**	CH_2Cl_2/RT/22	**3aa**, 72	−32
2	**CPA-2**	CH_2Cl_2/RT/22	**3aa**, 88	−14
3	**CPA-3**	CH_2Cl_2/RT/22	**3aa**, 43	−22
4	**CPA-4**	CH_2Cl_2/RT/22	**3aa**, 60	−28
5	**CPA-5**	CH_2Cl_2/RT/22	**3aa**, 34	−12
6	**CPA-6**	CH_2Cl_2/RT/22	**3aa**, 61	−11
7	**CPA-7**	CH_2Cl_2/RT/22	**3aa**, 84	−59
8	**CPA-8**	CH_2Cl_2/RT/22	**3aa**, 83	−56
9	**CPA-9**	CH_2Cl_2/RT/22	**3aa**, 82	72
10	**CPA-9**	EtOAc/RT/46	**3aa**, 86	67
11	**CPA-9**	$PhCH_3$/RT/46	**3aa**, 92	75
12	**CPA-9**	$PhCF_3$/RT/46	**3aa**, 90	35
13	**CPA-9**	PhCl/RT/46	**3aa**, 85	67
14	**CPA-9**	$PhCH_3$/−20/46	**3aa**, 88	87
15	**CPA-9**	CH_2Cl_2/−20/46	**3aa**, 99	87
16[d]	**CPA-9**	DCE/−20/46	**3aa**, 88	82
17	**CPA-9**	$PhCH_3$/−40/19	**3aa**, 47	87
18[e]	**CPA-9**	CH_2Cl_2/−40/48	**3aa**, 92	92
19[e]	**CPA-9**	CH_2Cl_2/−60/48	**3aa**, 90	93

[a]Unless noted, a mixture of **1a** (0.05 mmol), **2a** (0.06 mmol), and **CPA** (5.0 mol %) in the solvent (0.5 mL) was stirred at the indicated temperature for the time given. [b]Isolated yield. [c]Determined by chiral-phase HPLC analysis. [d]DCE = $ClCH_2CH_2Cl$. [e]**CPA-9** (10 mol %).

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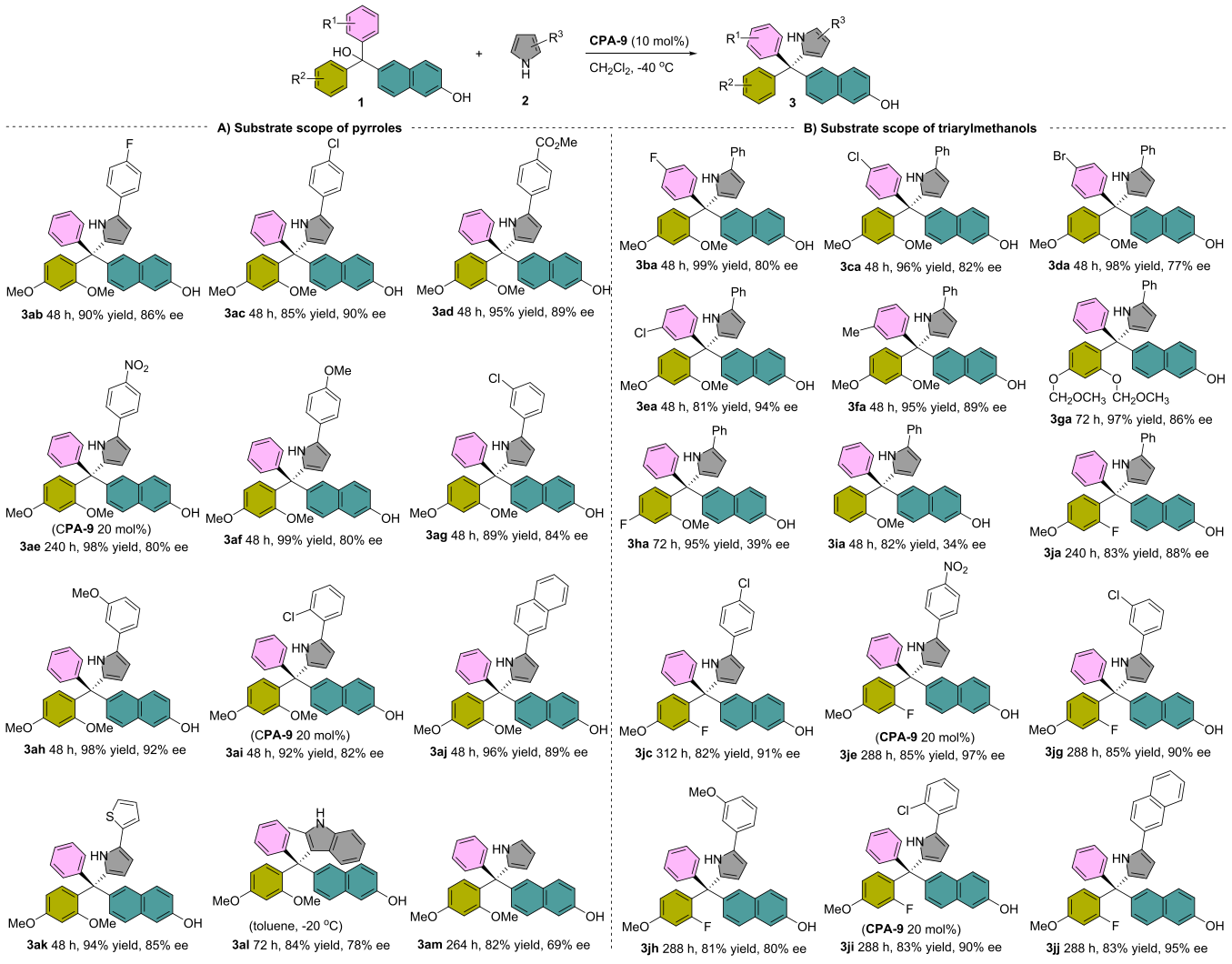
Table 2. Scope of Reaction between Triarylmethanols 1 and Pyrroles 2[a]



[a]Unless noted, a mixture of **1** (0.05 mmol), **2** (0.06 mmol), and **CPA-9** (10.0 mol %) in CH_2Cl_2 (0.5 mL) was stirred at −40 °C for the indicated time. Products **3** were obtained in isolated yield. The ee was determined by chiral-phase HPLC analysis.

Table 2A, a wide range of pyrroles **2** bearing various substituents (R^3) reacted smoothly with triarylmethanol **1a** to afford the corresponding tetraarylmethanes **3** in generally high to excellent yields and enantioselectivities. In detail, the reaction of 4-halophenyl-1*H*-pyrroles **2b**,**c** furnished the desired products **3ab** in 90% yield with 86% ee and **3ac** in 85% yield with 90% ee, respectively. 2-Aryl-1*H*-pyrroles with strong electron-drawing group **2d**,**e** also reacted smoothly to give tetraarylmethane **3ad** in 95% yield with 89% ee and **3ae** in 98% yield with 80% ee (**CPA-9** 20 mol %, 240 h). Furthermore, 2-aryl-1*H*-pyrrole with electron-donating group **2f** was also compatible, affording product **3af** in 99% yield with 80% ee. Moreover, the position of the substituent on the aromatic ring had a slight effect on the reaction and tetraarylmethanes **3ag**−**ai** were obtained in 89−98% yield with 82−92% ee. The reaction of bulky 2-(naphthalen-2-yl)-1*H*-pyrrole **2j** generated tetraarylmethane **3aj** in 96% yield with 89% ee. Notably, the use of 2-(thiophen-2-yl)-1*H*-pyrrole **2k** enabled the formation of tetraarylmethane **3ak** in 94% yield with 85% ee. Particularly, the desired tetraarylmethane **3al** was also obtained in 84% yield with 78% ee from the reaction of 2-methylindole **2l** in toluene at −20 °C after 72 h. Exceptionally, 1*H*-pyrrole **2m** afforded the desired product **3am** in 82% yield with 69% ee due to the minor stereodifferentiation among aromatic groups. Encouragingly, we then investigated the substrate scope of triarylmethanols (Table 2B). Notably, the catalytic system was also amenable to a series of triarylmethanols **1b**−**f** with different substituents (R^1), delivering the tetraarylmethanes **3ba**−**fa** in 81−99% yields with 77−94% ee. Besides the suitable reaction partners and catalytic system, the stereodifferentiation among aromatic groups of triarylmethanols is also a key point to successful stereocontrol. Replacing methoxyl with an OCH_2OCH_3 group (R^2) led to the formation of tetraarylmethane **3ga** in 97% yield with 86% ee. The enantioselectivity decreased dramatically when *p*-methoxyl was replaced by fluoro or hydrogen, triarylmethanol **1h** furnishing **3ha** in 95% yield with 39% ee, and triarylmethanol **1i** furnishing **3ia** in 82% yield with 34% ee. Importantly, the desired product **3ja** was obtained in 83% yield with 88% ee from the **CPA-9** catalyzed reaction of 6-[(2-fluoro-4-methoxyphenyl)(hydroxy)(phenyl)methyl]-naphthalen-2-ol **1j**. Furthermore, a series of pyrroles were successfully applied in the **CPA-9**-catalyzed reaction of triarylmethanol **1j**, affording the desired tetraarylmethanes

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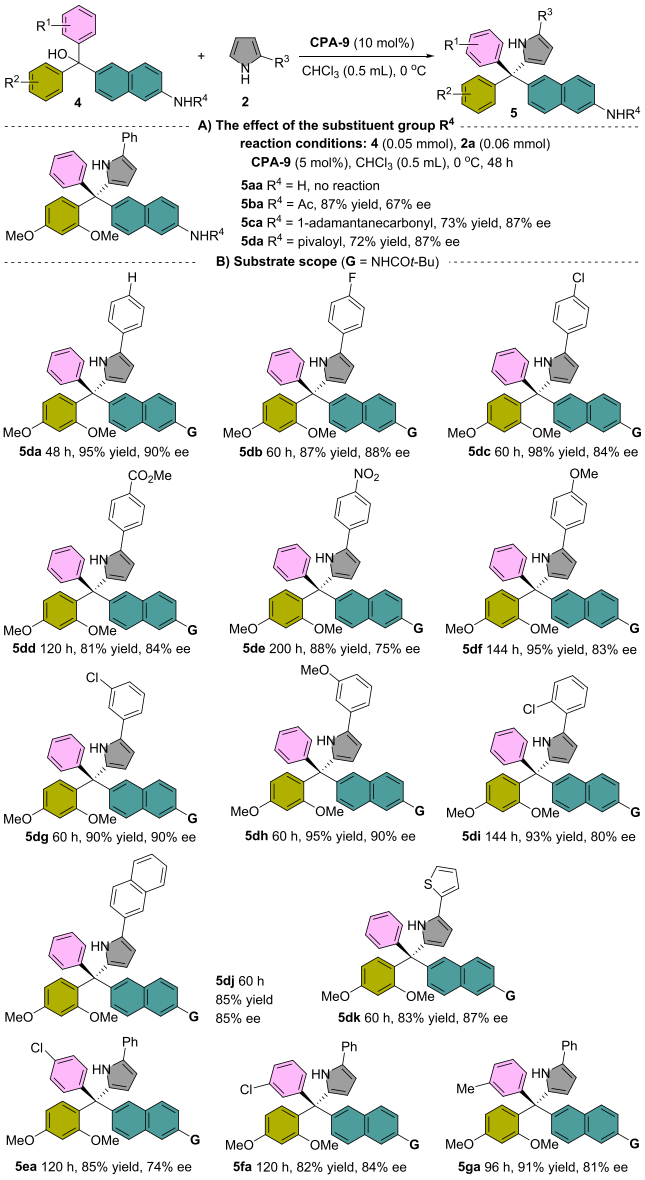
3jc, **3je**, and **3jg**−**jj** in 81−85% yields with 80−97% ee. Notably, these encouraging data indicated that the enantioselectivity could be maintained at a high level by the proper stereodifferentiation among aromatic groups of triarylmethanols. Taken altogether, these results not only verified that the 2-naphthol unit was a practical auxiliary group to in situ form an $\alpha,\beta,\gamma,\delta,\varepsilon,\zeta$-conjugate system followed by asymmetric 1,8-addition by chiral PA catalysis but also indicated that organocatalytic enantioselective synthesis of tetraarylmethanes was achieved via the **CPA-9**-catalyzed formal nucleophilic substitution reaction of functionalized tertiary alcohols.

Subsequently, we turned our attention to the **CPA-9** catalyzed reaction of 6-(hydroxydiarylmethyl)naphthalen-2-amines **4**. Pleasingly, satisfying results were obtained after the initial investigations on the effect of solvent and the substituent group (R^4) of triarylmethanols (Table 3A, see the SI for details). Notably, the desired tetraarylmethanes **5da** were obtained in 72% yields with 87% ee. Importantly, further modifying parameters enabled the formation of product **5da** in 95% yield with 90% ee (Table 3B). Generally, a broad scope of pyrroles **2** was compatible to furnish products **5db**−**dk** in 81−98% yields with 75−90% ee. Moreover, triarylmethanols with different substituents **4e**−**g** were also accommodated to afford the desired tetraarylmethanes **5ea**−**ga** in 82−91% yields with 74−84%. Confirmed by these results, the naphthalen-2-amine unit was also a practical auxiliary group, enabling the achievement of organocatalytic enantioselective synthesis of tetraarylmethanes from naphthalen-2-amine-based tertiary alcohols.

The reaction could be easily scaled up without compromising the efficiency and enantioselectivity (Scheme 2A). Transformations of tetraarylmethane **3aa** were also achieved (Scheme 2B). Methylation of hydroxyl afforded product **3la** in 92% yield with 88% ee. Esterification of tetraarylmethane **3aa** formed product **6aa** in 81% yield with 84% ee. Furthermore, functional group transformations respectively furnished product **7aa** in 83% yield and **3ka** in 90% yield without losing enantioselectivity. Control experiments were also investigated (Scheme 2C). Not surprisingly, the reaction between triarylmethanol **1 k** and 2-phenyl-1*H*-pyrrole **2a** afforded the corresponding tetraarylmethane **3ka** in 85% yield but with a poor enantioselectivity (23% ee). When the phenolic hydroxyl group was blocked by the methyl group, replacing triarylmethanol **1a** with triarylmethanol **1l** resulted in the formation of product **3la** in 88% yield with 71% ee. Moreover, the **CPA-9**-catalyzed reaction between triarylmethanol **1a** with 1-methyl-2-phenyl-1*H*-pyrrole **2n** afforded the corresponding product **3an** in 58% yield with 14% ee. These results indicated that both the free hydroxyl group on the naphthalene and free amino group on pyrrole played key roles in controlling the stereoselectivity.

The absolute configuration of product **3aa** was assigned by comparison between its experimental and calculated ECD spectra to be the *R* configuration (Figure 1). The survey of the non-linear effect indicated that there is a linear relationship between the enantiopurity of product **3aa** and that of catalyst **CPA-9**, suggesting that it is likely that one catalyst molecule is involved in the enantiodetermining transition state (Figure 2). Based on the **CPA-9**-catalyzed reaction between triarylmethanol **1a** and 2-aryl-1*H*-pyrrole **2b**, kinetic studies indicated that this reaction exhibited a first order in triarylmethanol **1a**, a first order in chiral catalyst **CPA-9**, and a zeroth order in nucleophile **2b** (Figure 3).

Table 3. Scope of Reaction between Triarylmethanols 4 and Pyrroles 2[a]



[a]Unless noted, a mixture of **4** (0.05 mmol), **2** (0.06 mmol), and **CPA-9** (10.0 mol %) in $CHCl_3$ (0.5 mL) was stirred at 0 °C for the time given. Products **5** were obtained in isolated yield. The ee was determined by chiral-phase HPLC analysis.

To better understand the mechanism and origins of stereoselectivity, DFT calculations were performed on the CPA-catalyzed reaction of **1a** and **2a** (see the SI for details). As shown in Figure 4A, the reaction was initiated by the formation of two relatively stable hydrogen bond complexes **I-*S*** and **I-*R*** from chiral phosphoric acid **CPA-9** and racemic substrate **1a** with 0.4 and 2.0 kcal/mol decreases in free energy, respectively. These intermediates **II** then undergo dehydration via transition states **TS1-*S*** and **TS1-*R*** to generate an identical intermediate 6-methylenenaphthalen-2(6*H*)-one **III** with corresponding energy barriers of 18.3 and 18.1 kcal/mol, respectively. Subsequently, the intermolecular nucleophilic addition of 2-phenyl-1*H*-pyrrole **2a** to intermediate **III** via transition states **TS2-*R*** with an energy barrier of 8.4 kcal/mol affords intermediate **IV-*R***. The subsequent intermolecular

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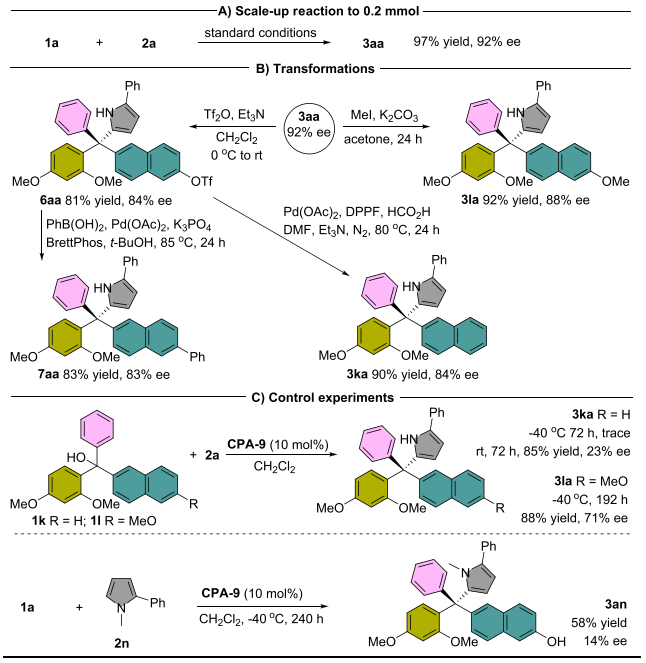
Scheme 2. Further Investigations



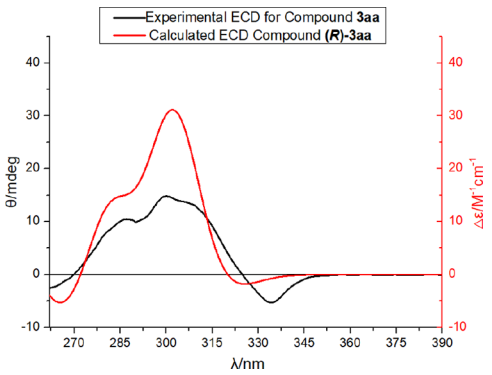


Figure 1. Comparison of the calculated ECD of compound (*R*)-**3aa** with the experimental one of compound **3aa**.

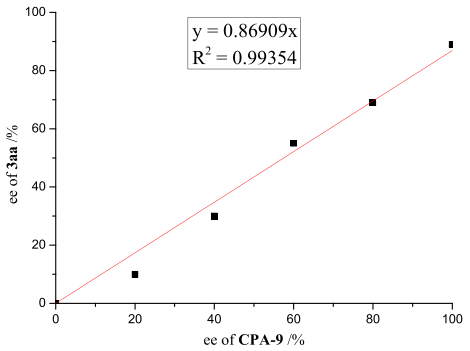


Figure 2. Non-linear effect.

proton transfer via transition state **TS3-*R*** with an energy barrier of 10.7 kcal/mol generates the final *R*-configured product **3aa** and regenerates the chiral phosphoric acid **CPA-9**. Notably, the enantioselectivity is determined by the intermolecular nucleophilic addition step, and the dehydration is considered to be the rate-determining step, which is consistent with kinetic studies. Alternatively, the intermolecular nucleophilic addition via transition state **TS2-*S*** with an energy barrier of 11.5 kcal/mol would reversibly generate intermediate **IV-*S***, which is the precursor of the *S*-configured product. The relative free energy of the transition state **TS2-*S*** is 3.1 kcal/mol higher than that of transition state **TS2-*R***, which indicates that the generation of the *S*-configured product is unfavorable. The calculated enantiomeric excess (ee) is 99% based on the energy difference between transition states **TS2-*R*** and **TS2-*S***, which slightly overestimated the experimental result (93% ee).

To further investigate the origins of enantioselectivity, optimized structures of transition states **TS2-*R*** and **TS2-*S*** were compared (Figure 4B). In transition state **TS2-*S***, there is potential steric repulsion between methoxy groups and the pyrenyl group of the catalyst as the methoxy group is orientated toward the pyrenyl group of the catalyst. In contrast, the methoxy groups are far away from the phenanthryl group of the catalyst in transition state **TS2-*R***, suggesting the absence of steric repulsion between the methoxy and the phenanthryl group of the catalyst. The steric repulsion in **TS2-*S*** resulted in a longer C−H···O−P hydrogen-bond distance (2.44 Å) and thus a weaker hydrogen-bonding interaction than that in transition state **TS2-*R*** (2.09 Å). Moreover, a more stable C−H···O−P hydrogen-bonding interaction was found in transition state **TS2-*R*** with contact distances of 2.05 Å. Therefore, these hydrogen bond interactions contributed to the stabilization of transition state **TS2-*R***, which were the most important factors in obtaining high enantioselectivity. Further calculations were done by removing the substituents of the catalyst with methyl groups, and then the single-point $\Delta\Delta E^{\ddagger}$ without optimization was computed. The calculated results show that the truncated structure of **TS2-*R*** is still 3.4 kcal/mol more stable than that of **TS2-*S***, indicating that hydrogen-bonding interactions play a leading role in determining high enantioselectivity.

CONCLUSIONS

In conclusion, an organocatalytic stereoconvergent formal nucleophilic substitution reaction of triarylmethanols with the 2-naphthol/naphthalen-2-amine unit as the auxiliary group has been developed for catalytic enantioselective construction of chiral tetraarylmethanes. Specifically, 6-methylenenaphthalen-2(6*H*)-ones and 6-methylenenaphthalen-2(6*H*)-imines were generated in situ from 6-(hydroxydiarylmethyl)naphthalen-2-ols and 6-(hydroxydiarylmethyl)naphthalen-2-amines, respectively, followed by CPA-mediated 1,8-conjugate addition of 2-aryl-1*H*-pyrroles to afford tetraarylmethanes in high to excellent yields with high enantioselectivities. Importantly, DFT calculations assisted the design of the auxiliary group of functionalized tertiary alcohols and were utilized to investigate the reaction mechanism. Different from the activating mechanism of QMs, a new catalytic model was developed to understand the origin of stereoselectivity. In addition to suitable reaction partners and the catalytic system, stereodifferentiation among aromatic groups was confirmed to be a key element to successful stereocontrol. Of note, not only the organocatalytic stereoconvergent formal nucleophilic substitution reaction of racemic triarylmethanols for enantioselective synthesis of chiral tetraarylmethanes but also organocatalytic stereoselective 1,8-additions of in situ formed *α,β,γ,δ,ε,ζ*-conjugate systems were achieved for the first time with the aid of either 2-naphthol or naphthalen-2-amine unit as the auxiliary group.

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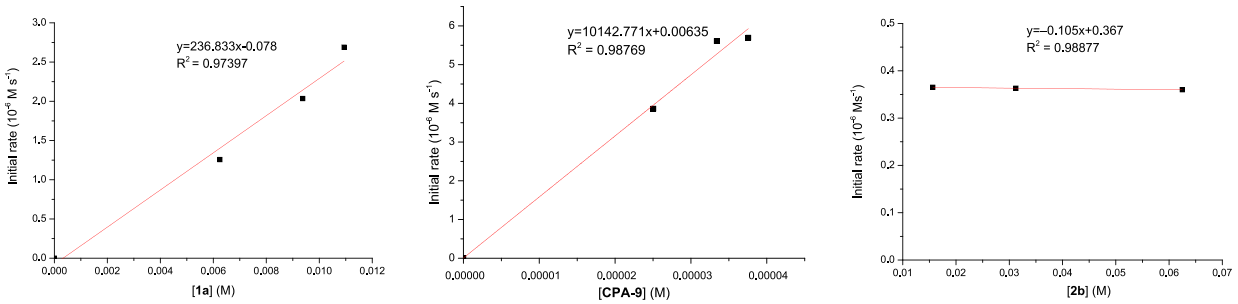

Figure 3. Kinetic studies.

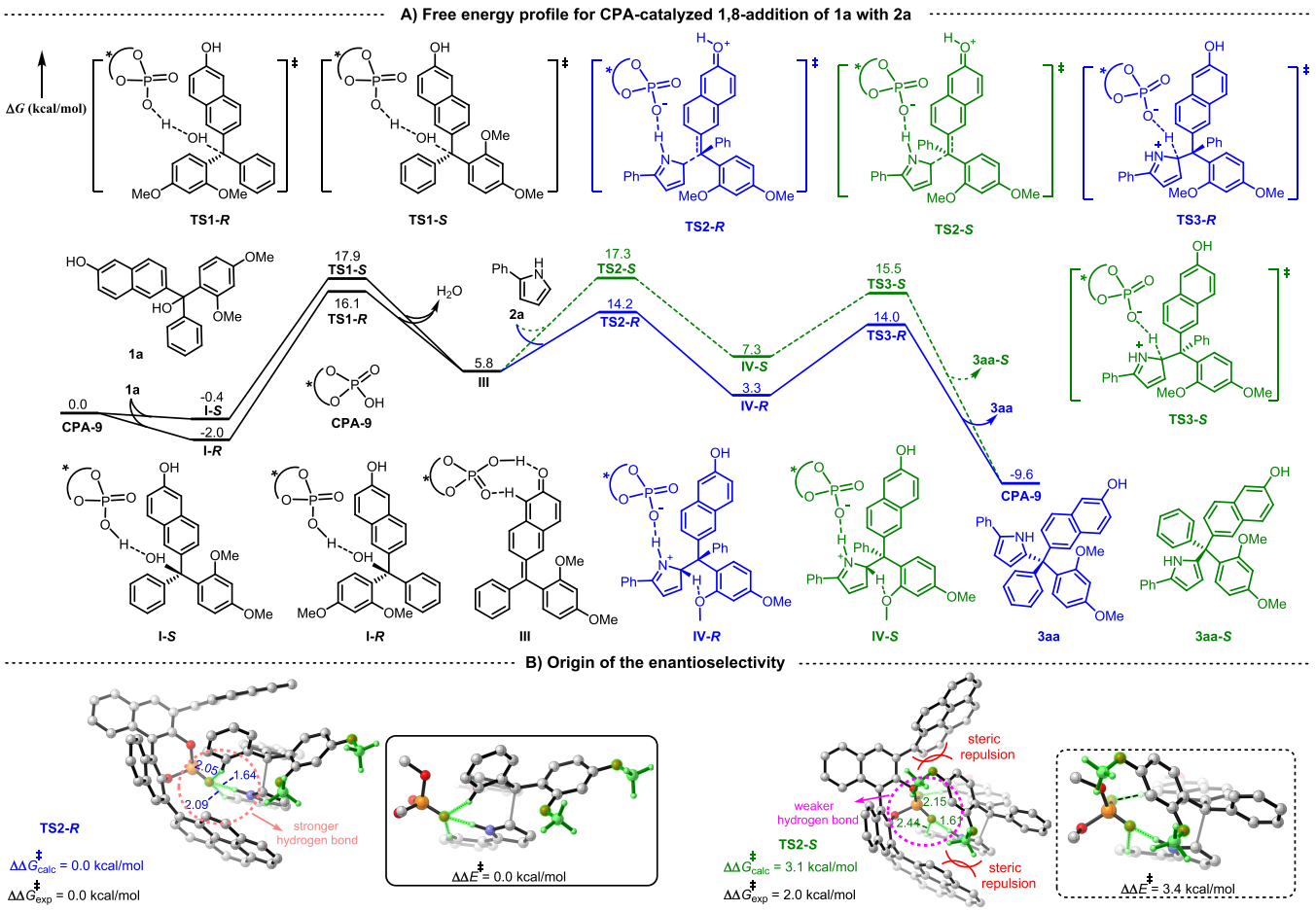

Figure 4. DFT study. The energy values are in given kcal/mol and represent the relative free energies calculated with the DFT/M06-2X method in dichloromethane. The distances are given in angstrom.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.3c05107.

Experimental section, characterization details, control experiment, non-linear effects, kinetic studies, copies of NMR spectra, computational investigations (PDF)

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Notes

The authors declare no competing financial interest.

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