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Access to Enantiopure Triarylmethanes and 1,1-Diarylalkanes by NHC-Catalyzed Acylative Desymmetrization

Shenci Lu[+], Xiaoxiao Song[+], Si Bei Poh, Hui Yang, Ming Wah Wong,*and Yu Zhao*

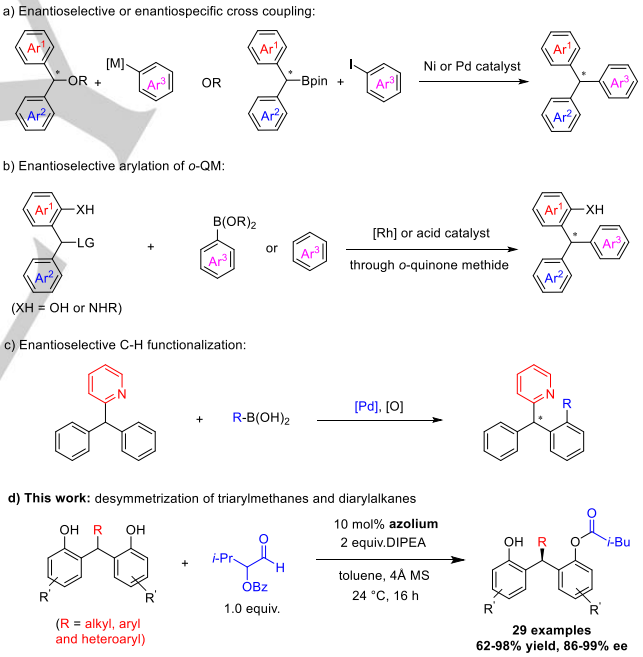
Abstract: We present here an unprecedented, efficient and enantioselective synthesis of triarylmethanes and 1,1-diarylalkanes through NHC-catalyzed acylative desymmetrization of bisphenols. This method utilizes readily available substrates, reagents and a simple procedure to deliver the valuable products in excellent enantiopurity. DFT calculations reveal that the selectivity is governed by the C-C bond cleavage step of the tetrahedral intermediate leading to the ester product. A transition state model featuring a combination of intramolecular hydrogen bond and steric effect is developed to explain the enantioselectivity.

Introduction

Triarylmethanes and 1,1-diarylalkanes are highly valuable structural motifs in pharmaceutical industry and material science.[1-2] The development of efficient catalytic methods to access these motifs in a stereoselective fashion has thus been the focus of substantial studies in the past decade.[3] The most established strategies for these efforts have focused on substitution reactions of the central benzylic carbon. In particular, transition metal-catalyzed cross coupling of a benzylic unit with an aryl group has been accomplished in both enantiospecific (using enantioenriched substrate)[4] and enantioselective[5] fashion (Scheme 1a).[6] Transition metal-catalyzed addition of aryl nucleophiles[7] or acid-catalyzed Friedel-Crafts reaction of arenes to electron deficient alkenes including *o*-quinone methide (Scheme 1b)[8] represents another successful type of reactions to deliver these compounds in high enantioselectivities.[9]

As an intriguing alternative strategy, the desymmetrization of achiral triarylmethanes and 1,1-diarylalkanes may enable efficient access to new analogs of these valuable compounds in an enantiopure form. Along these lines, the Yu group reported an elegant Pd-catalyzed enantioselective C-H arylation (Scheme 1c).[10] In this system, however, pyridine is required as the directing group on the substrate. A general preparation of enantiopure triarylmethanes as well as diarylalkanes by desymmetrization is still highly desired.

NHC-catalyzed conversion of aldehydes to activated carboxylates has been developed into a powerful strategy for enantioselective C-C bond formation[11] as well as kinetic resolution of the alcohol counterpart.[12] Our group has developed highly enantioselective acylative kinetic resolution of oxindole-derived tertiary alcohols as well as axially chiral BINOL and NOBIN analogs.[12e-g] We were curious whether NHC-catalyzed enantioselective acylation of phenols could be applied to the desymmetrization of a wide range of triarylmethanes and 1,1-diarylalkanes (Scheme 1d). This method, if successful, will also represent an important advancement on controlling remote prochiral stereogenic centers. It is noteworthy that the Miller group reported a classical example of highly enantioselective acylation of distant bisphenols catalyzed by a nucleophilic peptide catalyst.[13] A bulky substituent such as *t*-butyl on the substrate was required for achieving high enantioselectivity in this system. Very recently, the Chi group also reported an elegant example of NHC-catalyzed bisphenol desymmetrization to access P-stereogenic phosphinates.[14] We report herein a highly efficient and general desymmetrization of triarylmethanes/1,1-diarylalkanes by NHC-catalyzed acylation of phenols.[14] This method utilizes readily available substrates, reagents and a simple procedure to deliver the valuable products in excellent enantiopurity. Further derivatization of the products could lead to additional structural diversity of these compounds. Experimental and DFT calculations have also provided key information on the origin of stereoselectivity of this catalytic system.



Scheme 1. Different Approaches to Enantioenriched Triarylmethanes

Results and Discussion

We initiated our studies by testing the enantioselective acylation of **1a** by screening different aldehyde reagents and chiral azolium salts as the pre-catalyst (Table 1). Excellent reactivity could be achieved in this catalytic system, so only 1.0 equiv. of aldehyde was used. As it turned out, the use of a bulkier aldehyde **2b** vs. **2a** led to the formation of **5a** with a higher ee of 93% (entry 2 vs. 1), while the leaving group on **2b** or **2c** made no difference on the reaction outcome at all (entry 2 vs. 3). The stable and easier-to-handle aldehyde **2c** was then chosen for further optimization.[15] Azolium **3a** remained as the

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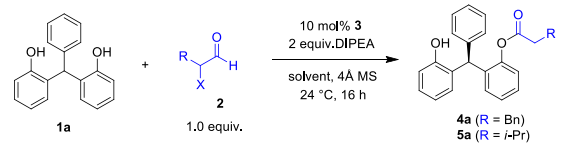
optimal choice after further screening of other pre-catalysts (entries 4-6). Fortunately, the screening of solvents identified that toluene could improve the enantioselectivity of **5a** to an excellent 97% (entry 9 vs. 3).

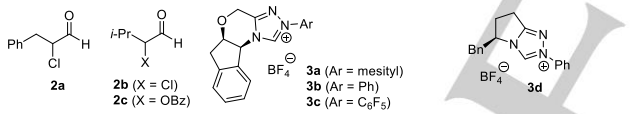
With the optimal conditions in hand, we moved on to examine the scope of this NHC-catalyzed acylative desymmetrization. It is important to note that *essentially all the prochiral substrates (both triarylmethanes and 1,1-diarylalkanes) could be prepared in a single step from commercial compounds* (see SI for details). The ready availability of substrates certainly renders this catalytic method more attractive for practical application.

Table 1. Optimization of the Reaction Conditions[a]



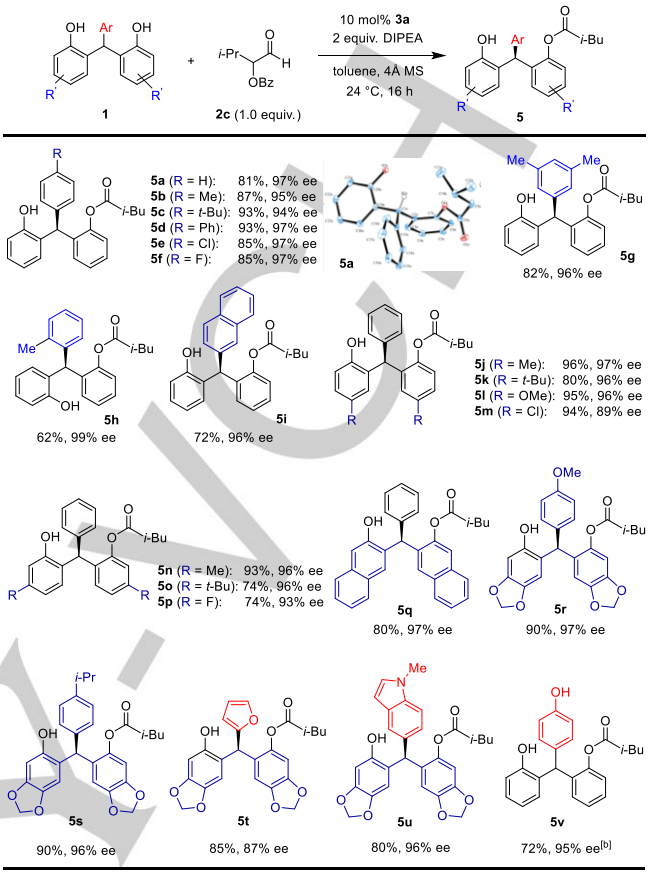
entry	aldehyde	NHC	solvent	yield (%)[b]	ee (%)[c]
1	**2a**	**3a**	DCM	**4a,** 90	55
2	**2b**	**3a**	DCM	**5a,** 80	93
3	**2c**	**3a**	DCM	**5a,** 80	93
4	**2c**	**3b**	DCM	**5a,** 80	88
5	**2c**	**3c**	DCM	**5a,** 77	59
6	**2c**	**3d**	DCM	**5a,** 70	5
7	**2c**	**3a**	CH_3CN	**5a,** 78	88
8	**2c**	**3a**	THF	**5a,** 80	92
9	**2c**	**3a**	toluene	**5a,** 81	97

[a] The reactions were carried out by mixing all reagents and catalysts under N_2. See supporting information for more details. [b] Isolated yield. [c] Determined by chiral HPLC.



As shown in Scheme 2, a range of substituted aryl groups could be tolerated to deliver **5a** to **5i** in uniformly high yield and excellent enantioselectivity (94-99% ee). In the case of **5h** bearing an *ortho*-substituted aryl group, the highest enantioselectivity was obtained albeit at the cost of relatively low yield. In addition, different substitution patterns on the bisphenol units were also well-tolerated. Products **5j**-**5s** were again obtained in uniformly high efficiency and selectivity. More importantly, various heteroarenes could serve as the substituent as well. While the smaller furan group resulted in slightly diminished enantioselectivity for **5t**, **5u** bearing an indole was obtained in the standard level of 96% ee. Lastly, an interesting trisphenol substrate was tested. Bisphenol **5v** was obtained in good yield and excellent ee. The chemoselectivity for the synthesis of **5v** is noteworthy: clearly the phenol on the *para*-position is more accessible for acylation. However, the two *ortho*-phenols seem to work in a cooperative fashion to result in the acylation of the more sterically hindered phenol selectively.

The absolute configuration of **5a** was established unambiguously by single crystal x-ray analysis and the configuration of the other products was assigned by analogy.



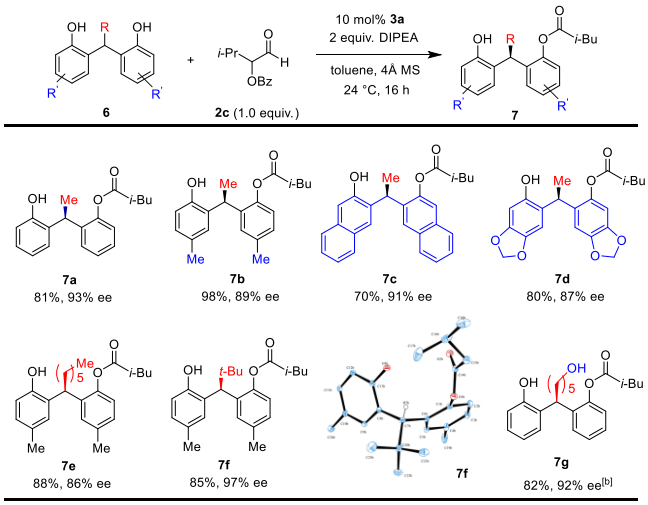
[a] See Table 1. [b] THF was used as the solvent for better solubility of the triol substrate.

Scheme 2. Scope of Triarylmethanes[a]

The broad substrate scope of triarylmethanes prompted us to examine the desymmetrization of 1,1-diarylalkanes under similar conditions as well (Scheme 3). For **6a** bearing a small methyl substituent, we were excited to observe a high ee of 93% for **7a**. Clearly this catalytic system has a high degree of tolerance for the steric size of the substituent on the benzylic carbon bearing two phenol units. Various analogs bearing substituted aryl groups including **7b** to **7d** were first examined. Good to high level of enantioselectivity could be obtained. On the other hand, 1,1-diarylalkane **7e** bearing a linear *n*-hexyl group could also be obtained in a good 86% ee. *t*-Butyl-containing **7f** could be obtained in an excellent ee of 97%. Another intriguing triol substate **6g** was also examined. Again, acylation of the phenol is favored over that of a primary alcohol to deliver **7g** in high yield with excellent ee. The absolute configuration of this series of products was further confirmed by single crystal x-ray analysis of **7f**, which was consistent with that of the triarylmethane series.

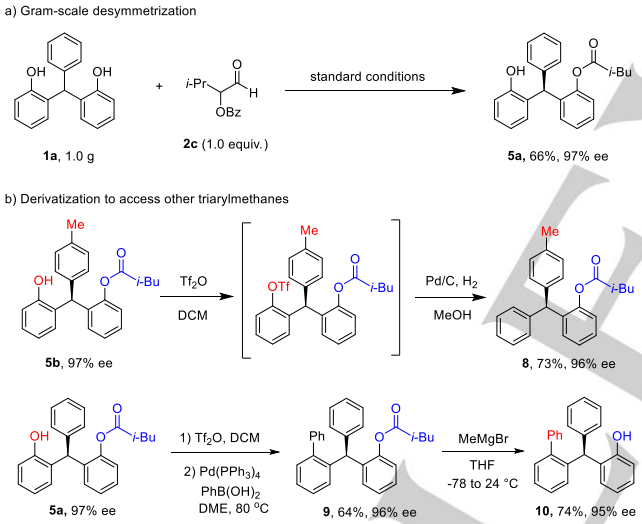
The presence of the phenol units in the substrates provided opportunities for further derivatization of the enantioenriched products obtained from the NHC-catalyzed desymmetrization. As shown in Scheme 4, gram-scale transformation of **1a** to **5a** worked out similarly well. Conversion of the free phenol in **5b** to the corresponding triflate followed by reduction led to the formation of **8** in good yield and excellent ee. Alternatively, **5a** could be converted to **9** by Suzuki coupling; the ester moiety could be reduced to yield **10** in good yield and high ee. Further derivatization of **10** is possible if desired. In this way, the

products in our studies can serve as a springboard for the access to more diverse triarylmethanes and 1,1-diarylalkanes.



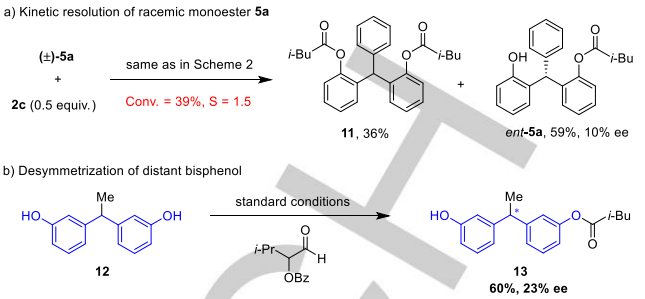
[a] See Table 1. [b] THF was used as the solvent for better solubility of the triol substrate.

Scheme 3. Scope of 1,1-Diarylalkanes [a]



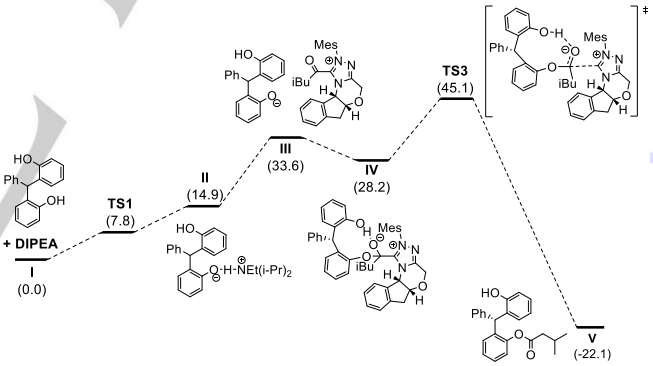
Scheme 4. Access to More Diverse Triarylmethanes

In our reaction, a small amount of bisester products could be obtained in some cases. When we tested the kinetic resolution of racemic **5a** (Scheme 5a), however, the NHC-catalyzed acylation resulted in minimal level of enantioselectivity for this process (S = 1.5). The enantioselectivity in our catalytic system, therefore, only comes from the desymmetrization step. This attempted kinetic resolution also provided further support for the cooperativity of the diol functionality in this catalytic system. The desymmetrization of a more distant bisphenol **12** was also attempted (Scheme 5b). Much lower level of reactivity as well as enantioselectivity was obtained for 13. The two phenols in this substrate may be too distant for any effective cooperative interaction.



Scheme 5. Substrate Structure Alternation

To shed light on the origin of the stereoselectivity, DFT calculations were carried out. A detailed computational study of the mechanism of desymmetrization of triarylmethane **1a** through **3a**-catalyzed acylation with aldehyde **2c** was performed (Scheme 6). Experimentally, the selectivity of this reaction was shown not to be affected by the method of generating the key acyl azolium intermediate **A** (entries 2 vs. 3, Table 1). Hence, we only investigated the steps after the formation of **A**. Density functional theory (DFT) calculations, using the Gaussian programs,[16] were performed at M06-2X/6-311+G**//M06-2X/6-31G* level.[17] Solvent effect was included using SMD implicit solvation method[18] and with toluene as solvent for both optimizations and single-point energy calculations. Unless otherwise noted, calculated relative free energies at 298 K (ΔG_{298}, in kJ/mol) were reported in the text. Images of reported structures were rendered using CYLview.[19]



Scheme 6. Proposed Mechanism for NHC-Catalyzed Acylation of **1a** and calculated reaction profile. Calculated relative energies (ΔG_{298}) for the desymmetrization of **1a** are shown in kJ/mol in the parentheses.

Our proposed catalytic mechanism is illustrated in Scheme 6. Since phenol and their derivatives are poor nucleophiles, they need to be activated by a base before they can be used in nucleophilic addition to acyl azolium. Thus, we first investigated the deprotonation of **1a** by a representative base DIPEA. The proton transfer process is calculated to be quite facile, with a small barrier of 7.8 kJ/mol (via transition state **TS1**), leading to an ion pair complex (**II**) that is 14.9 kJ/mol higher in energy than **I** (Scheme 6). The calculated result is typical of low-barrier hydrogen bonds proposed for many important enzymatic systems where the proton is shared between two heteroatoms whose pKa's are closely matched.[20] The presence of a low-barrier hydrogen bond suggests that the base is not involved in the stereo-determining step of the overall catalytic reaction.

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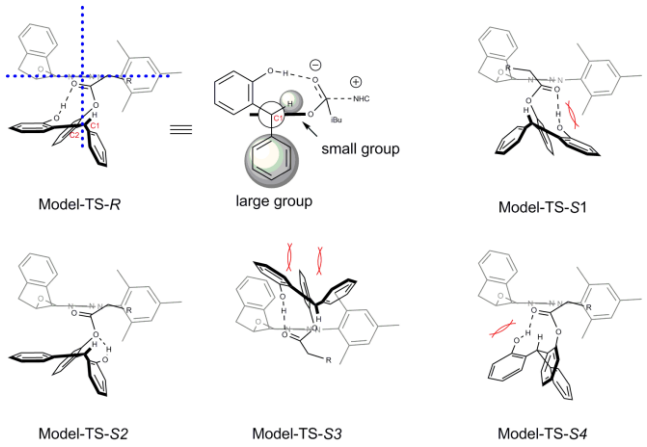


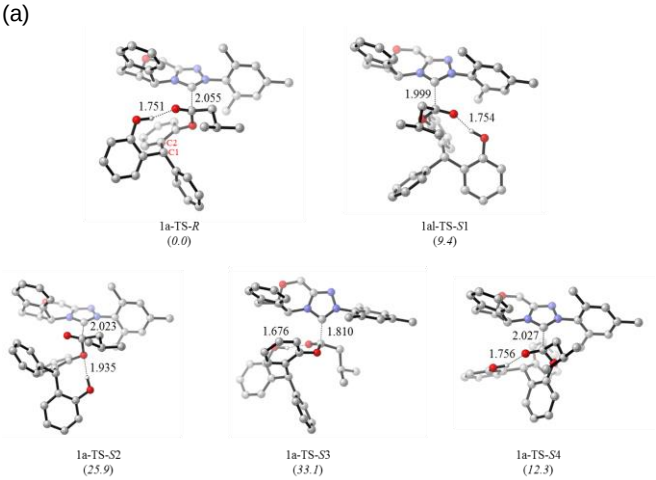
Figure 1. Proposed Transition State Models. The Newman Projection of **Model-TS-*R*** is also shown.

The ion pair complex **II** can undergo an ion exchange with acyl azolium **A** to yield another ion-pair intermediate **III**. However, we were unable to locate a definite transition state (**TS2**) for the subsequent C-O bond-forming step. Extensive potential energy surface scans show that the potential energy surface is extremely flat in the vicinity of the complex **III**, indicating it is only tangibly stable and might not have a significant role for the overall reaction dynamics. In other words, our calculations suggest that the ion pair complex **III** would most likely collapse instantly to form an oxyanion tetrahedral intermediate (**IV**), which is 5.4 kJ/mol lower in energy, upon contact of each other. Similar issue has been reported in DFT studies of NHC-catalyzed annulation reaction and Michael addition.[21] In comparison, C-C bond cleavage of the tetrahedral intermediate **IV** to yield the ester product **V** and regenerate the NHC catalyst is calculated to have a significant activation barrier of 16.9 kJ/mol, via transition state **TS3**. Assuming there is a fast equilibrium between acyl azolium **A** and the tetrahedral intermediate **IV**,[22] the C-C bond cleavage step being irreversible, with product **V** being 67.2 kJ/mol lower in energy than the tetrahedral intermediate **IV**, and Curtin-Hammett paradigm of stereocontrol,[23] we postulated that the stereoselectivity of NHC-catalyzed desymmetrization of triarylmethanes can be determined from the relative energy of various TSs of the C-C bond cleavage step. Subsequently, we examined various possible transition states (**TS3**) of this key step to shed light on the origin of stereoselectivity.

Next, we constructed transition state models based on the structures of the oxyanion intermediate IV, which is characterized by a strong intramolecular hydrogen bond, and the ester product, which adopts the *Z* conformation. The *in situ* generated NHC catalyst in this study does not possess a hydrogen bond donor or acceptor that can interact with either the aldehyde or triphenyl moiety in the stereo-determining step. Thus, the mode of chiral induction by the catalyst is likely of steric interaction. To view the spatial arrangement of atoms of the catalyst moiety, schematic representations in the stereo-determining TS's are shown in Figure 1. The vicinity of the carbonic carbon atom of NHC in these TS's can be divided into four quadrants, three of which are crowded with phenyl and mesityl groups of the catalyst moiety, leaving the quadrant opposing the phenyl group relatively free of steric hindrance. We hypothesized that the lowest energy *R*-inducing transition state adopts a conformation (see Figure 1, Newman project) such that the large group (e.g. phenyl of **1a**) on carbon C1, which will become the stereogenic center of the product, is furthest away from the catalyst moiety and the second phenol group forms an important intramolecular hydrogen bond to the partially negatively charged carbonyl oxygen (**Model-TS-R**). For comparison, four possible low-lying *S*-inducing transition states could be envisioned. Three of them, namely **Model-TS-S1**, **Model-TS-S3** and **Model-TS-S4**, while maintaining the critical hydrogen bond, incur significant steric repulsion to the catalyst moiety. Although the third *S*-inducing transition state, namely **Model-TS-S2**, may also fit into the empty quadrant of the catalyst moiety, it is proposed to have a weaker hydrogen bond to the less negatively charged oxygen atom of the leaving ester.

To validate our proposed transition state model and to test its predictability, we selected a few substrates in such a way that their experimental ee's gave a large range so as to reduce the chance of false positive error. The various optimized TS structures for substrate **1a** and their relative enthalpies $\Delta\Delta H^{\neq}_{298}$ are shown in Figure 2, while computational results for other substrates are given in Table 2. These calculations lent strong support to our hypothesis that only the leaving ester leading to the *R*-ester product can fit into the empty quadrant and at the same time maintain the crucial intramolecular hydrogen bond to partially negatively charged oxygen atom (Figure S2 in SI). In the case of **1a**, the strength of the intramolecular hydrogen bond is estimated to be ~50 kJ/mol in transition state **1a-TS-R** (Figure S3 in SI). There are two low-energy *S*-inducing transition states, **1a-TS-*S*1** and **1a-TS-*S*4**, which are 9.4 and 12.3 kJ/mol higher in energy, respectively. The other two *S*-inducing transition states, namely **1a-TS-*R*2** and **1a-TS-*R*3** are both significantly higher in energy, by 25.9 and 33.1 kJ/mol, respectively. Based on these calculated results, we opted to focus on the lowest energy TS **1a-TS-*S*1** to unravel the origin of enantioselectivity. Overlay of the **1a-TS-*R*** and the mirror image of the lowest *S*-inducing transition state **1a-TS-*S*1** (Figure 2b) revealed that the mesityl moiety of the catalyst and the acylated phenol moiety of **1a** in **1a-TS-*S*1** are very close to each other. The closest C-H···C distance between the two in **1a-TS-*S*1** was measured to be 2.648 Å, shorter than sum of the van der Waals radii of 2.9 Å. To give a semi-quantitative understanding of the interaction, we performed NBO steric analysis[24] of **1a-TS-*S*1**, which showed a destabilizing interaction of 15.9 kJ/mol, suggesting the energy difference between the two TSs is mostly due to this steric interaction. To further support our transition state models, we compared calculated *ee*, based on the energy difference between **1a-TS-*R*** and **1a-TS-*S*1**, to experimental *ee* for **1a**, and they matched each other closely (entry 1, Table 2).

(a)



(b)

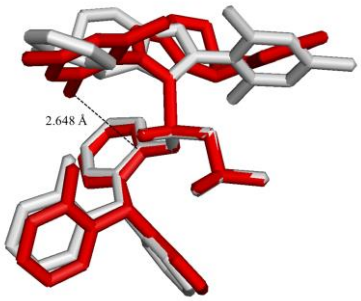
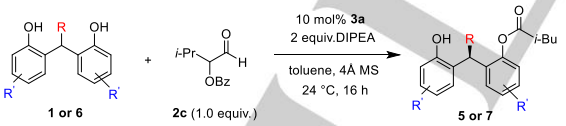


Figure 2. Optimized Transition State Geometries. Part a: optimized transition state geometries for desymmetrization of **1a**. Relative enthalpies ($\Delta\Delta H^{\neq}_{298}$) were reported in kJ/mol. Part b: overlay of **1a-TS-*R*** (white) and mirror image of **1a-TS-*S*1** (red) showing the closeness between the mesityl moiety of the catalyst and the acylated phenol moiety of **1a** in **1a-TS-*S*1**. Hydrogen atoms are not shown for clarity.

Although we have established the importance of steric interaction to the origin of enantioselectivity, we want to emphasize that the role of intramolecular hydrogen bonds in TSs should not be underestimated. They help to rigidify transition state conformation by restricting rotation around the important single bond between C2 and C1 (Figure 2) and thus limit the number of accessible conformers, so that enantiomeric discrimination could be possible. The large group on C1 could help to further rigidify the TSs. Experimentally, when the large group was changed from a methyl group to a *t*-butyl group, entries 6 and 7 of Table 2, or from a phenyl group to an *o*-tolyl group, entries 1 and 2 of Table 2, enantioselectivity increased. The trend that bigger group on C1 gives higher enantioselectivity was well reproduced by calculations using our transition state model. Hence, the origin of stereoselectivity for desymmetrization of triarylmethanes is determined to be a combination of conformational rigidity due to strong intramolecular hydrogen bond and the steric requirement of the large group on C1, and the resulting unfavorable steric interaction between the mesityl group of the catalyst moiety and the acylated phenol moiety in **Model-TS-*S*1** (Figure S4 in SI).

Table 2. Predicted and Experimental Selectivity[a]



entry	substrate	$\Delta\Delta H^{\neq}$	calc *ee* (%)	expt *ee* (%)
1	**1a**	9.4	96	97
2	**1h**	11.0	98	99
3	**1l**	11.3	98	96
4	**1m**	8.5	94	89
5	**1t**	7.9	92	87
6	**6a**	10.7	97	93
7	**6f**	13.6	99	97

[a] Predicted *ee* calculated at M06-2X/6-311+G**//M06-2X/6-31G* level, using a two-TS model, namely **Model-TS-*R*** and **Model-TS-*S*1** (toluene solvent). Relative enthalpies ($\Delta\Delta H^{\neq}$) were reported in kJ/mol.

Conclusions

We have developed a highly efficient NHC-catalyzed acylative desymmetrization of remote bisphenols that provides access to a wide range of enantioenriched triarylmethanes and diarylalkanes. The simple procedure coupled with the uniformly high enantioselectivity makes this method a useful tool in organic synthesis. DFT calculations show that the selectivity is governed by the C-C bond cleavage step of the tetrahedral intermediate to yield the ester product. Transition state models involving a key intramolecular hydrogen bond between the tetrahedral intermediate oxygen and the remaining phenol and steric control from the catalyst moiety were successfully developed and generalized to desymmetrization of this important class of bisphenols.

Experimental Section

To a 4 mL vial was added **1** or **6** (0.075 mmol), triazolium salt **3a** (0.0075 mmol) and 4Å MS (50 mg). The mixture was taken into the glovebox, where aldehyde **2c** (12 μL, 0.075 mmol), anhydrous toluene (1.0 mL) and DIPEA (36 μL, 0.15 mmol) were added. The reaction mixture was taken outside the glovebox. The vial was then sealed and the reaction mixture was allowed to stir for 16 h. The crude reaction mixture was directly purified by silica gel column chromatography with hexanes/ethyl acetate (10:1 v/v) as eluent to afford the ester product.

Acknowledgements

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Keywords: acylation • desymmetrization • triarylmethanes • 1,1-diarylalkanes• *N*-heterocyclic carbene

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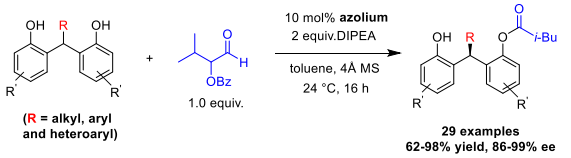

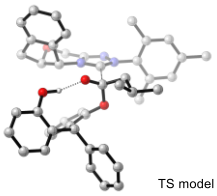

Efficient access to enantiopure triarylmethanes and diarylalkanes
TS model featuring H-bond and steric effect to explain stereoselectivity

Shenci Lu, Xiaoxiao Song, Si Bei Poh, Hui Yang, Ming Wah Wong, and Yu Zhao

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Access to Enantiopure Triarylmeth and 1,1-Diarylalkanes by NHC-Cata Acylative Desymmetrization

We present here a general, efficient and enantioselective synthesis of triarylmethanes and 1,1-diarylalkanes through NHC-catalyzed acylative desymmetrization of bisphenols. This method utilizes readily available substrates, reagents and a simple procedure to deliver the valuable products in excellent enantiopurity. DFT calculations provided a transition state model featuring a combination of intramolecular hydrogen bond and steric effect to explain the enantioselectivity.