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# Organocatalytic Asymmetric Synthesis of 1,1-Diarylethanes by Transfer Hydrogenation

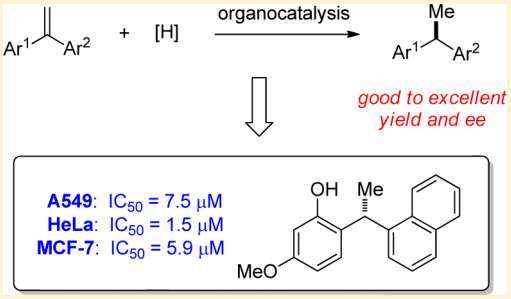
Zhaobin Wang,[†] Fujin Ai,[‡] Zheng Wang,[†] Wanxiang Zhao,[†] Guangyu Zhu,*[,‡] Zhenyang Lin,*[,†] and Jianwei Sun*[,†]

[†]Department of Chemistry, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China

[‡]Department of Biology and Chemistry, City University of Hong Kong, Kowloon Tong, Hong Kong SAR, China

Supporting Information

**ABSTRACT:** A new organocatalytic transfer hydrogenation strategy for the asymmetric synthesis of 1,1-diarylethanes is described. Under mild conditions, a range of 1,1-diarylethanes substituted with an *o*-hydroxyphenyl or indole unit could be obtained with excellent efficiency and enantioselectivity. We also extended the protocol to an unprecedented asymmetric hydroarylation of 1,1-diarylalkenes with indoles for the synthesis of a range of highly enantioenriched 1,1,1-triarylethanes bearing acyclic all-carbon quaternary stereocenters. These diaryl- and triarylethanes exhibit impressive cytotoxicity against a number of human cancer cell lines. Preliminary mechanistic studies combined with DFT calculations provided important insight into the reaction mechanism.




## INTRODUCTION

1,1-Diarylalkane is an important structural unit in numerous biologically active natural products and synthetic molecules, including a number of notable pharmaceuticals (e.g., tolterodine and sertraline).[1,2] Among them, unsymmetrically substituted 1,1-diarylethanes are particularly noteworthy because of their versatile applications in potential treatment of a wide range of diseases, such as insomnia, autoimmune disorders, inflammation, cancers, obesity, etc. (representative structures **I**–**V** shown Figure 1).[2]

As a result of the significance of these important diarylmethine pharmacophores, the development of efficient strategies for their enantioselective synthesis has been the focus of intense investigations.[3−5] A variety of state-of-the-art catalytic protocols have been developed, among which C($sp^2$)−C($sp^3$) cross-coupling (Scheme 1a) and hydrogenation of 1,1-diarylalkenes (Scheme 1b) represent the two major strategies that have been pursued with general success. However, although significant progress has been achieved, additional new efficient

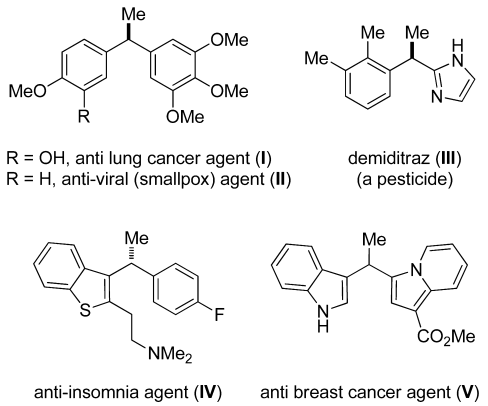
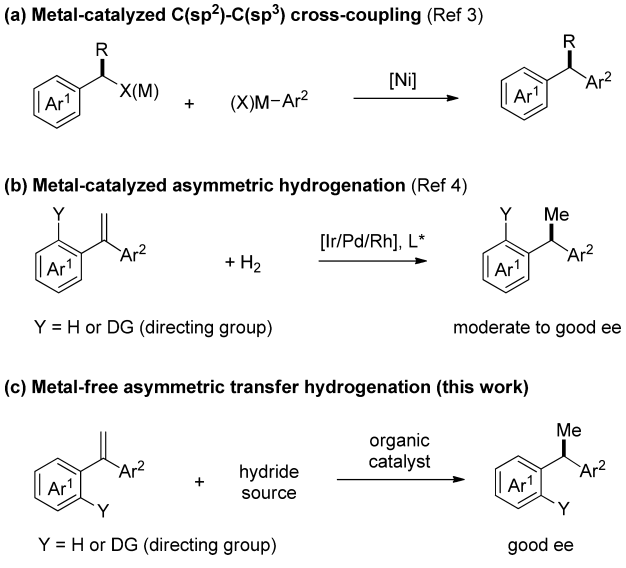



**Figure 1.** Representative bioactive 1,1-diarylethanes.

**Scheme 1. Typical Strategies for 1,1-Diarylmethine Stereocenter Formation**

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catalytic systems remain in high demand. Of particular note is the fact that the majority of these known strategies are based on metal catalysis, and removal of trace metal residues in pharmaceutical manufacturing processes is often tedious and costly. Herein we report a metal-free asymmetric transfer hydrogenation strategy for the synthesis of 1,1-diarylethanes with high efficiency and enantioselectivity (Scheme 1c) as well as the identification of a lead compound with impressive inhibitory activity against a number of cancer cell lines.

In the past decade, organocatalytic asymmetric transfer hydrogenation (ATH) has evolved as an attractive metal-free biomimetic alternative to the metal-based approaches.[6] A number of functional groups (e.g., ketimines, ketones, electron-deficient olefins) can be smoothly reduced with high enantioselectivity under mild conditions. A variety of elegant cascade processes involving ATH have also been designed to provide rapid access to highly enantioenriched heterocycles. Nevertheless, there still remain challenges in this field. For example, unactivated and electron-rich olefins have met with limited success. Specifically, to our knowledge, the ATH of 1,1-diarylalkenes lacking an electron-withdrawing group has not been realized in general. However, in contrast to metal-catalyzed hydrogenation, where reactivity is generally trivial but differentiation of the two aryl groups for chiral induction is challenging, organocatalytic ATH in this scenario would require solutions to both challenges (reactivity and chirality).

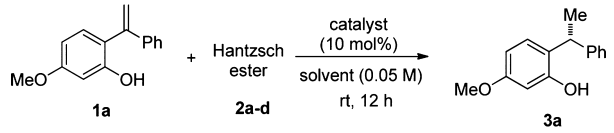
## RESULTS AND DISCUSSION

To overcome the above challenges, we resorted to a possible removable directing group on one of the two aryl groups.[7] In our initial study, a hydroxyl group was installed in the model substrate **1a**. Fortunately, with the Hantzsch ester **2a** as the hydride donor, the transfer hydrogenation of **1a** in the presence of a chiral phosphoric acid catalyst proceeded smoothly to provide the desired 1,1-diarylethane **3a** in generally excellent yield (Table 1).[8] Moderate to good enantioselectivity was observed with various chiral phosphoric acid catalysts. Among them, the BINOL-derived acid **A1** provided the best results.[9] Other Hantzsch esters and reaction solvents were also effective but with either reduced yield or diminished enantioselectivity. The use of 4 Å molecular sieves (MS) slightly increased the enantioselectivity. Reduced loading of the catalyst (to 5 or 2.5 mol %) or the hydride donor (to 1.5 equiv) did not result in significant erosion of the reaction efficiency or enantioselectivity (entries 16−18).

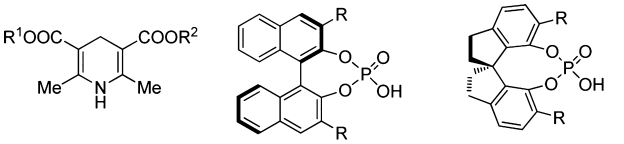
With the established protocol, we next examined the reaction scope. As shown in Scheme 2, a range of 1,1-diarylethylenes all smoothly participated in the asymmetric transfer hydrogenation to afford the corresponding 1,1-diarylethanes in high yield. For easy purification, most of the products were protected with a TMS group after treatment of the reaction mixture with TMSCl and $Et_3N$. It is noteworthy that the diarylmethine tertiary stereocenters were mostly generated with excellent stereocontrol. The mild conditions can tolerate a range of functional groups, including silyl ethers, alkenes, alkynes, thioethers, etc. It is also worth noting that the C═C bonds in **3d** and **3j** were not reduced under the standard conditions, demonstrating chemoselectivity and highlighting the effect of the directing group.

Furthermore, we were also interested in evaluating the generality of our protocol for indole-substituted 1,1-diarylethylenes (e.g., **4a**; Scheme 3), considering the fact that indole-containing compounds are versatile synthetic building blocks and useful

**Table 1. Reaction Optimization**[a]




| entry | catalyst | reductant | solvent | yield (%)[b] | ee (%) |
|---|---|---|---|---|---|
| 1 | (*R*)-**A1** | **2a** | $CH_2Cl_2$ | 99 | 98 |
| 2 | (*R*)-**A2** | **2a** | $CH_2Cl_2$ | 92 | 68 |
| 3 | (*R*)-**A3** | **2a** | $CH_2Cl_2$ | 92 | 82 |
| 4 | (*R*)-**B1** | **2a** | $CH_2Cl_2$ | 91 | −97 |
| 5 | (*R*)-**B2** | **2a** | $CH_2Cl_2$ | 89 | −76 |
| 6 | (*R*)-**B3** | **2a** | $CH_2Cl_2$ | 97 | −96 |
| 7 | (*R*)-**B4** | **2a** | $CH_2Cl_2$ | 98 | −77 |
| 9 | (*R*)-**A1** | **2b** | $CH_2Cl_2$ | 94 | 98 |
| 10 | (*R*)-**A1** | **2c** | $CH_2Cl_2$ | 98 | 96 |
| 11 | (*R*)-**A1** | **2d** | $CH_2Cl_2$ | 94 | 96 |
| 12 | (*R*)-**A1** | **2a** | $CHCl_3$ | 99 | 95 |
| 13 | (*R*)-**A1** | **2a** | THF | 27 | 98 |
| 14 | (*R*)-**A1** | **2a** | EtOAc | 38 | 98 |
| 15 | (*R*)-**A1** | **2a** | toluene | 88 | 95 |
| 16[c,d] | (*R*)-**A1** | **2a** | $CH_2Cl_2$ | 99 | 99 |
| 17[c,e] | (*R*)-**A1** | **2a** | $CH_2Cl_2$ | 84 | 97 |
| 18[c,d,f] | (*R*)-**A1** | **2a** | $CH_2Cl_2$ | 97 | 98 |




**2a** $R^1 = R^2 = Et$
**2b** $R^1 = R^2 = Me$
**2c** $R^1 = R^2 = {}^tBu$
**2d** $R^1 = Me$; $R^2 = {}^tBu$

**A1**: R = $SiPh_3$
**A2**: R = 2,4,6-$(^iPr)_3C_6H_2$
**A3**: R = 9-anthryl
**A4**: R = 2,6-$(^iPr)_2$-4-(Ad)$C_6H_2$

**B1**: R = 3,5-$(CF_3)_2C_6H_3$
**B2**: R = 9-phenanthryl
**B3**: R = 2,4,6-$(^iPr)_3C_6H_2$
**B4**: R = 9-anthryl

[a]Reaction scale: **1a** (0.1 mmol), **2** (2 equiv), catalyst (10 mol %), solvent (2.0 mL), rt, 12 h. [b]GC yields with *n*-decane as the internal standard. [c]Run with 4 Å MS as an additive. [d]5 mol % catalyst loading. [e]2.5 mol % catalyst loading. [f]Run with 1.5 equiv of **2a**.

subunits in numerous natural products and biologically active molecules.[10] However, under the standard conditions, the reaction of **4a** proceeded with disappointingly low enantioselectivity (49% ee), although a clean conversion to the desired transfer hydrogenation product **5a** was observed. The enantioselectivity could not be significantly improved simply by lowering the reaction temperature (59% ee at −30 °C) or using a different catalyst. In contrast to those substrates in Scheme 2, **4a** does not have an *o*-hydroxy directing group, which is presumably the reason for the increased difficulty in stereocontrol. Driven by the importance of this type of indole product, we screened a wide range of conditions. After considerable effort, we were pleased to find that with benzothiazoline **6** as the reductant and **A2** as the catalyst, the asymmetric transfer hydrogenation of **4a** proceeded with both high chemical efficiency and excellent enantioselectivity (91% yield, 91% ee).[11] This new standard protocol is general for the synthesis of a range of indole-substituted 1,1-diarylethanes (**5b−e**; Scheme 3). To the best of our knowledge, general and efficient asymmetric hydrogenation of indole-substituted 1,1-diarylalkenes of this type is unknown.[12]

As depicted in Scheme 4, we have proposed a possible reaction mechanism. The electron-rich styrene substrate **1** is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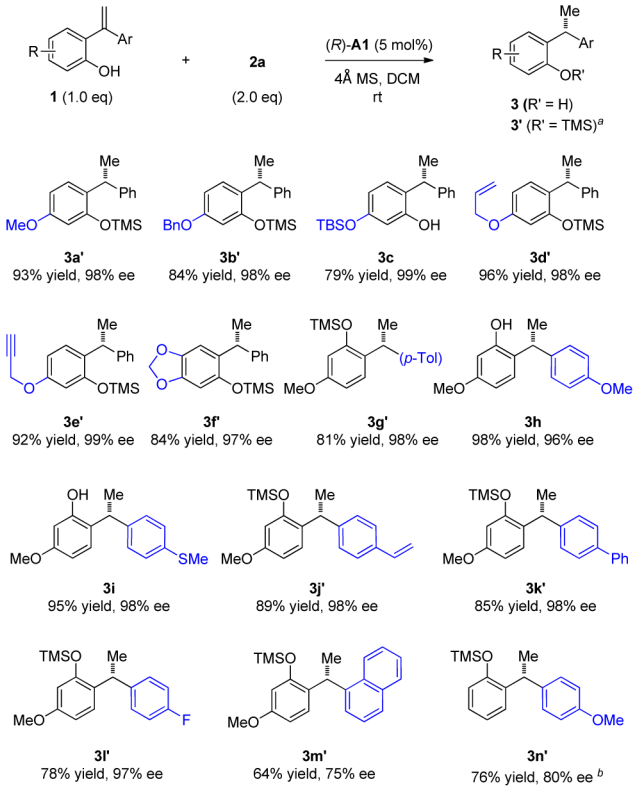
**Scheme 2. Scope Study of the ATH Reaction**[a]



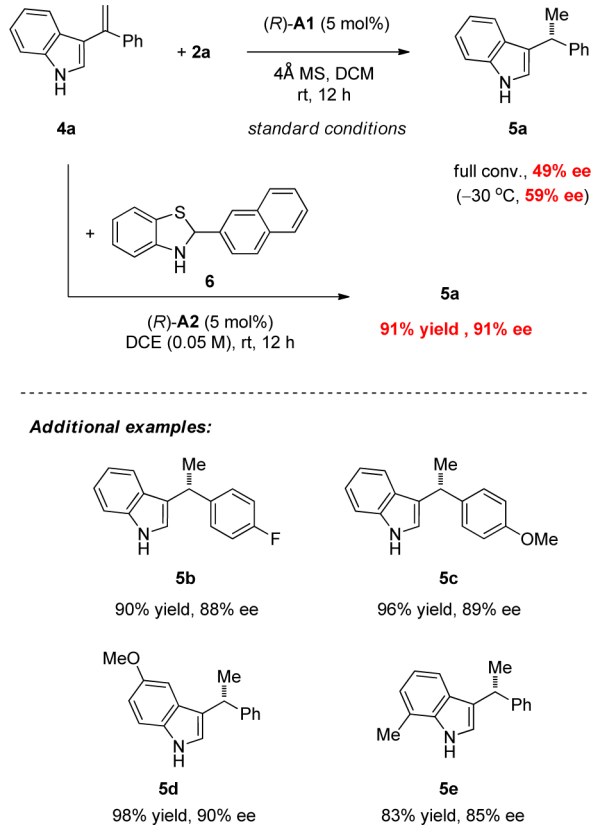

[a]Products **3** have $R_f$ values very close to that of the pyridine byproduct (from oxidation of **2a**). To simplify purification, the reaction mixtures were treated with TMSCl and $Et_3N$ upon completion. The corresponding silyl ethers were obtained as the products (except for **3c**, **3h**, and **3i**). [b]Run at 60 °C for 5 days.

initially protonated by the catalyst to form the tertiary carbocation intermediate **IM-R1**, in which the chiral phosphate anion also interacts with the hydroxyl directing group via hydrogen bonding. The ionic form has a neutral resonance structure **IM-R2**, which is an activated *o*-quinone methide (*o*-QM) form. The two resonance structures are the two extreme forms of the actual intermediate regarding electron density distribution. Presumably the intermediate is more represented as the activated *o*-QM form in nonpolar organic solvents (e.g., DCM). Subsequent hydride addition forms the observed product and regenerates the chiral acid catalyst.[13] The stereochemistry is controlled by the chiral anion (as in chiral ion-pairing catalysis) or the chiral acid (as in hydrogen-bonding catalysis).

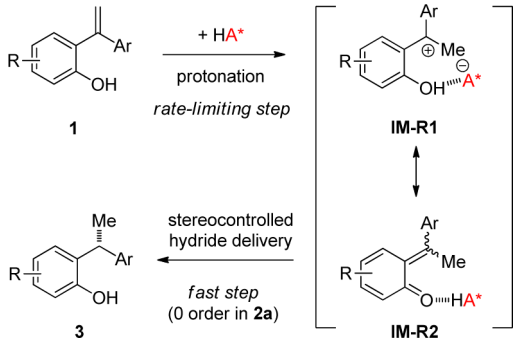
To gain further insight into the reaction mechanism, particularly on the major form of the intermediate and the absolute stereocontrol, we carried out B3LYP-D3 density functional theory (DFT) calculations.[9] First of all, the simplified structures of the possible intermediates (*E*)- and (*Z*)-**IM′** employing a biphenyl-based phosphoric acid were calculated (Figure 2). The distinct bond lengths of the C−C bonds in the six-membered ring clearly indicate that the intermediate should indeed be more represented as an activated *o*-QM (**IM-R2**), in contrast to the essentially equal bond lengths expected in the aryl ring of the ionic form (**IM-R1**).

Notably, although the *E* isomer is more stable than the *Z* isomer (+2.1 kcal/mol), the barrier for the formation of (*Z*)-**IM′** is lower than that for (*E*)-**IM′** ($\Delta\Delta G^{\ddagger}$ = 2.0 kcal/mol). More importantly, the first step (i.e., the formation of the QM

**Scheme 3. Reactions of Indole-Substituted Olefins**




**Scheme 4. Possible Reaction Mechanism**



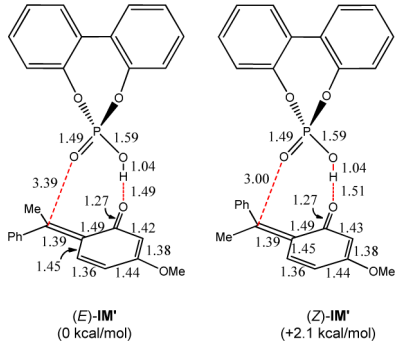




**Figure 2.** DFT-calculated structures of the simplified intermediate (**IM′**).

intermediate) is rate-determining, and the subsequent hydride addition is a fast step. The results were also confirmed by experiments. Indeed, kinetic studies indicated that the reaction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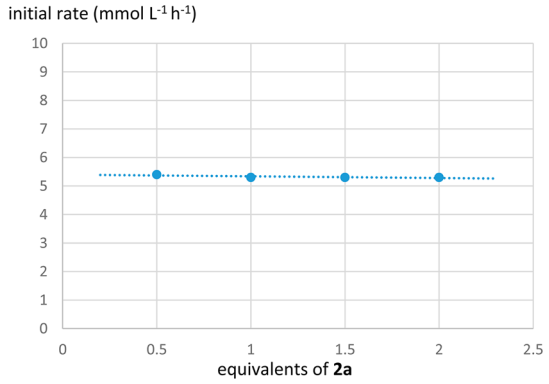
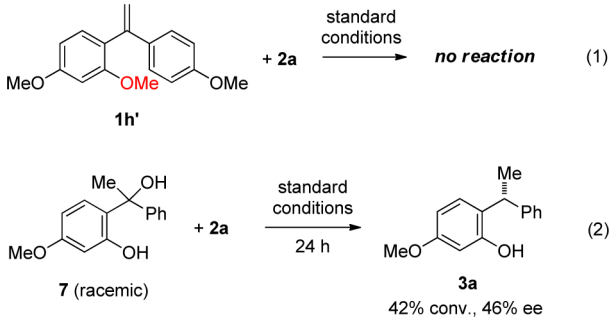



**Figure 3.** Zeroth-order kinetics of Hantzsch ester **2a**.

is zeroth-order in Hantzsch ester **2a** (Figure 3). Isotope-labeling experiments also showed that the first step is irreversible.[9] Thus, the *Z* isomer, though less stable, is preferentially generated for subsequent rapid hydride addition.

DFT calculations also indicated that in the transition state of the hydride addition, the Hantzsch ester N–H has a hydrogen-bonding interaction with the catalyst phosphoryl oxygen, and thus, the hydride is delivered to the side of the (*Z*)-*o*-QM plane where the catalyst resides.[14] This rationale is also consistent with the observed absolute stereochemical outcome.[15]

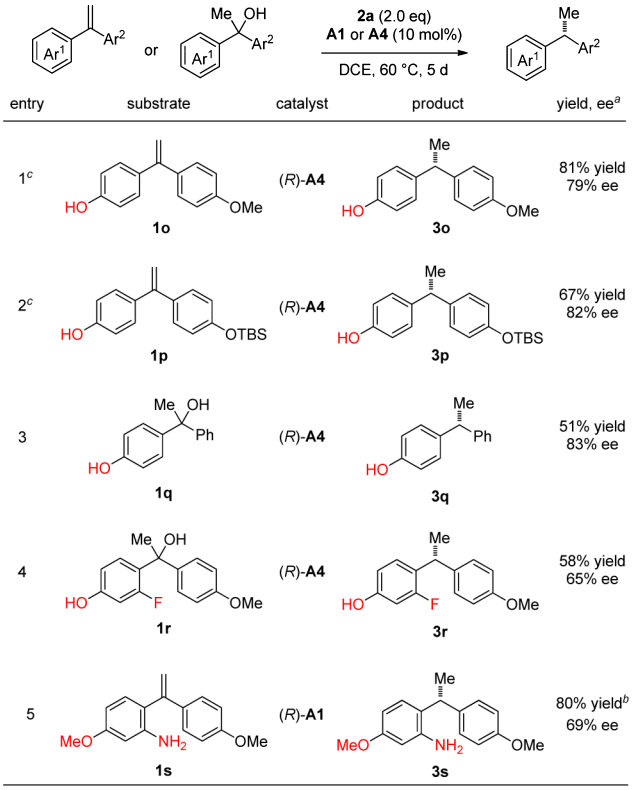
To further probe the reaction mechanism, we performed some control experiments. We protected the free *o*-hydroxyl directing group and subjected the analogue **1h′** to the standard conditions. No reaction was observed (eq 1), thereby confirming




the importance of the free hydroxyl group that is required to form the *o*-QM intermediate. Furthermore, we also employed racemic tertiary alcohol **7** as the substrate, which can potentially generate the common *o*-QM intermediate after protonation followed by loss of a water molecule.[16] Indeed, the same 1,1-diarylethane **3a** was generated under the standard conditions, but the reaction proceeded with a much lower rate and the enantioselectivity was also much lower (42% conversion, 46% ee; eq 2). We believe that the generation of the *o*-QM intermediate is relatively slow compared with the situation using **1a** as the starting material. Moreover, in the first step, the selectivity (barrier difference) for the formation of the (*Z*)-QM and (*E*)-QM intermediates might not be as good as that with **1a**, thereby compromising the product enantiomeric excess.

Aiming to further expand the scope of the reaction, we examined additional substrates without an *o*-hydroxyl directing group (Table 2). Although the previous standard conditions could not be directly applied to achieve good enantioselectivity, presumably because of the loss of the anchoring group for effective stereocontrol, subsequent extensive conditions optimization

**Table 2. Other Substrates without an *o*-Hydroxy Group**




[a]The remainder of the mass balance is the styrene starting material or the corresponding styrene from dehydration (entries 3 and 4). The products from entries 1, 3, and 4 have $R_f$ values very similar to those of the remaining styrenes, so these yields are NMR yields. [b]Isolated yield. [c]Run for 3 days.

identified that with catalyst **A4**, substrates with a *p*-hydroxyl group could smoothly react to form the desired hydrogenation products with good enantioselectivity (entries 1 and 2). Under the same conditions, racemic tertiary alcohols **1q** and **1r** were also suitable substrates. In view of the above mechanistic analysis, we believe that these reactions might involve the intermediacy of *p*-quinone methides (*p*-QMs). The observed low reaction rate in these cases could be explained by the ineffective synergistic activation and delivery of the Hantzsch ester nucleophile to the remote $\delta$ position of the *p*-QMs, considering that the primary activation by the bifunctional catalyst is located at the *p*-oxygen moiety (carbonyl of the *p*-QM). However, the stereocontrol in these cases remained reasonably good, particularly in view of the remote control in the absence of an ortho anchoring group. It is worth mentioning that catalytic asymmetric reactions of *p*-QMs with high enantioselectivity are very scarce and remain challenging.[17] In particular, those with $\delta,\delta$-disubstituted *p*-QMs are essentially unknown. Finally, *o*-aminostyrene **1s** could also participate in the asymmetric transfer hydrogenation to form **3s** (entry 5).

Finally, in addition to the use of Hantzsch esters as the reaction partners, we also evaluated indole nucleophiles, hoping to achieve a formal asymmetric hydroarylation of the 1,1-diarylethylenes. Gratifyingly, subjection of **1a** and indole to the standard conditions formed the desired triarylethane **8a**, but with a low reaction rate (~50% conversion, 48 h) and moderate enantioselectivity (76% ee) (Scheme 5). It is worth noting that chiral 1,1,1-triarylalkanes represent another important family of pharmacophores in medicinal chemistry, particularly with an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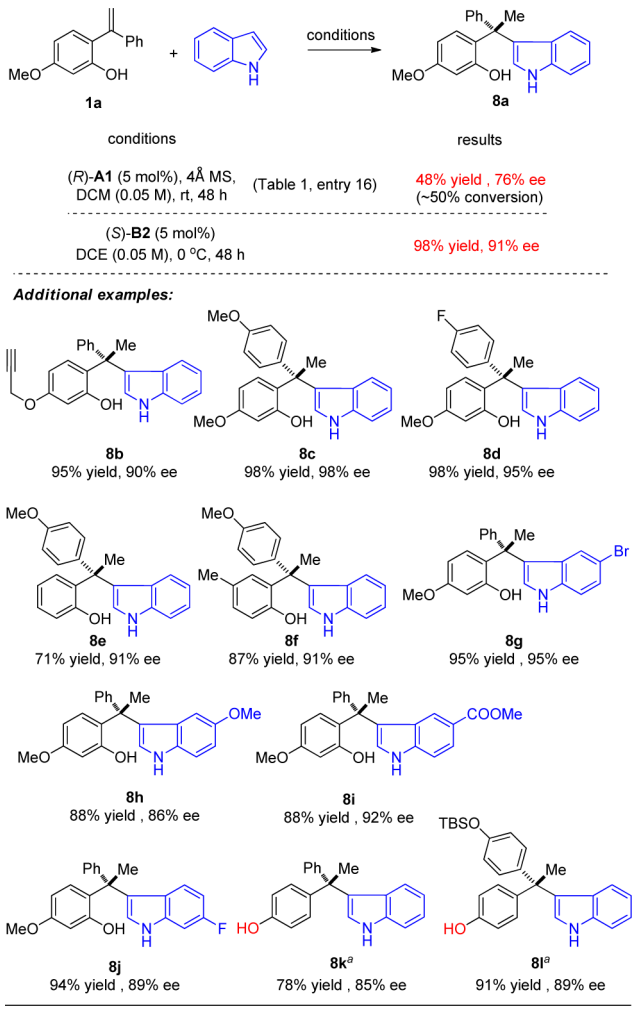
**Scheme 5. Asymmetric Hydroarylation of 1,1-Diarylalkenes 1 with Indoles**[a]

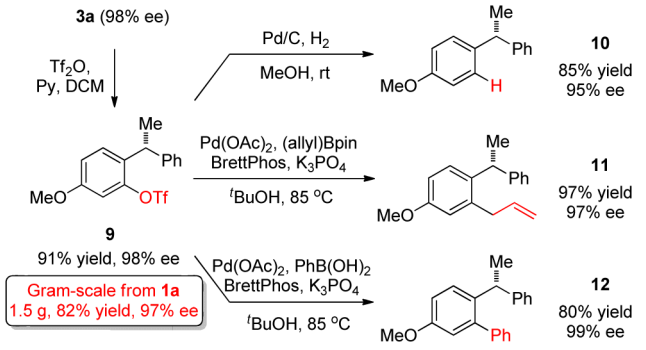



[a]Run with 10 mol % (*S*)-**B3** at 60 °C for 4 days.

indole moiety incorporated.[10,18] Aiming to improve the reaction results, we did some optimization of the reaction conditions and finally found that the SPINOL-derived acid (*S*)-**B2** could catalyze the transformation with both excellent efficiency and enantioselectivity (98% yield, 91% ee). Thus, the reaction represents a new asymmetric alkene hydroarylation to form all-carbon quaternary stereocenters.[19,20] A brief scope study indicated that the new conditions are general, and a range of highly functionalized indole-containing triarylethanes were obtained with excellent efficiency and enantioselectivity, including those lacking a *p*-alkoxy group (**8e** and **8f**) or an *o*-hydroxyl group (**8k** and **8l**).

We also carried out some derivatizations of the transfer hydrogenation product **3a**, particularly to verify the removable/convertible feature of the hydroxyl directing group. **3a** could easily be converted to aryl triflate **9** (Scheme 6). Under Pd-catalyzed hydrogenation conditions, the triflate moiety was removed under mild conditions to form **10** in 85% yield. In addition, the aryl triflate can undergo smooth cross-coupling reactions to install an allyl or phenyl group with excellent efficiency. Notably, in all of these transformations the diarylmethine stereocenter was essentially not touched. A gram-scale two-step reaction from **1a** also delivered triflate **9** in good

**Scheme 6. Transformations of the ATH Product 3a**




overall yield with excellent enantioselectivity, demonstrating the reliability of the protocol.

We were intrigued by the potential biological activities of these diaryl- and triarylalkanes,[2] and thus, we randomly selected a number of our reaction products for the evaluation of cytotoxicity in different human cancer cells, including A549 (lung cancer), HeLa (cervical cancer), and MCF-7 (breast cancer). The results are summarized in Table 3. In human lung

**Table 3. Cytotoxicities in Human Cancer Cells**

| | $IC_{50}$ ($\mu$M)[a] | | |
|---|---|---|---|
| compound | A549 | HeLa | MCF-7 |
| **3d** | 32.6 ± 4.6 | nd | nd |
| **3b** | 25.9 ± 2.8 | 26.6 ± 0.8 | 25.3 ± 1.2 |
| **3j** | 35.1 ± 1.5 | nd | nd |
| **3l** | 42.0 ± 4.2 | nd | nd |
| **3g** | 33.2 ± 2.6 | nd | nd |
| **3m** | 7.5 ± 0.6 | 1.5 ± 0.2 | 5.9 ± 0.7 |
| **8a** | 26.7 ± 2.2 | 21.7 ± 0.8 | 19.3 ± 6.4 |
| **8c** | 17.9 ± 4.8 | nd | nd |
| **8d** | 26.1 ± 1.0 | nd | nd |
| Dox[b] | 0.21 ± 0.06 | 0.07 ± 0.01 | 0.05 ± 0.01 |

[a]$IC_{50}$ values were measured by an MTT assay upon 72 h drug treatment. Values were obtained through independent measurement of cell viabilities. nd = not determined. [b]Doxorubicin (Dox) was used as a positive control.

cancer cells, most of the tested compounds exhibited cytotoxicity with median inhibitory concentration ($IC_{50}$) values in the micromolar range. Compounds **3b**, **3m**, and **8a** also effectively inhibited the proliferation of human cervical and breast cancer cells. Notably, **3m** showed impressive cytotoxicity in all of these cancer cells with $IC_{50}$ values in the low micromolar range.[21] The cell viability upon treatment with **3m** is shown in Figure 4. The results suggest that compound **3m** and its analogues might be promising anticancer agents for further investigation.

## CONCLUSION

We have demonstrated a new organocatalytic transfer hydrogenation strategy for the efficient asymmetric synthesis of 1,1-diarylethanes, an important family of compounds with broad medicinal and agricultural applications. With suitable design of the substrates by employing a removable *o*-hydroxyl group, we were able to achieve excellent reaction efficiency as well as asymmetric induction under mild conditions. Preliminary mechanistic studies confirmed the critical importance of the free hydroxyl group, which is required for the in situ generation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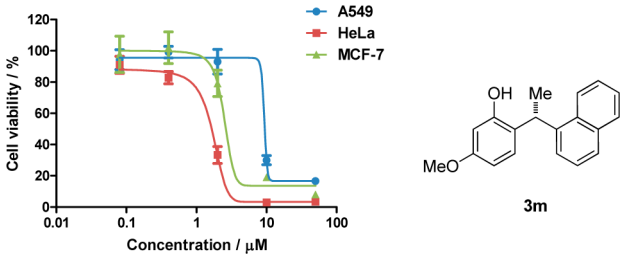


**Figure 4.** Viability of A549, HeLa, and MCF-7 cells upon treatment with **3m**.

of the *o*-quinone methide intermediate. DFT calculations provided important insight into the reaction mechanism. The free hydroxyl group in the products can be easily removed or converted to other useful functional groups. Furthermore, after careful modifications of the reaction conditions, we also successfully extended the protocol to the asymmetric transfer hydrogenation of a range of indole-substituted 1,1-diarylethylenes as well as styrenes without a directing group. Further extension of the protocol to asymmetric hydroarylation of 1,1-diarylalkenes with indoles was also successfully achieved, featuring efficient formation of the intermolecular C−C bonds and the challenging acyclic all-carbon quaternary stereocenters with excellent stereocontrol. Finally, a preliminary biological study indicated that the enantioenriched diaryl- and triarylalkanes obtained from our reactions exhibit impressive cytotoxicity against a number of human cancer cell lines. Further investigations of biological activities and mechanisms are underway.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental and computational details, bioactivity study, and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Authors

sunjw@ust.hk
chzlin@ust.hk
guangzhu@cityu.edu.hk

### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) For 1,1-diarylalkanes, see: (a) Hills, C. J.; Winter, S. A.; Balfour, J. A. *Drugs* **1998**, *55*, 813−820. (b) Silva, D. H. S.; Davino, S. C.; de Moraes Barros, S. B.; Yoshida, M. *J. Nat. Prod.* **1999**, *62*, 1475−1478. (c) McRae, A. L.; Brady, K. T. *Expert Opin. Pharmacother.* **2001**, *2*, 883−892. (d) Kainuma, M.; Kasuga, J.-i.; Hosoda, S.; Wakabayashi, K.-i.; Tanatani, A.; Nagasawa, K.; Miyachi, H.; Makishima, M.; Hashimoto, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3213−3218. (e) Stelmach, J. E.; Keith, R.; Parmee, E. R.; Tata, J. R. Patent WO 2006/102067 A1, 2006. (f) Kim, R. M.; Parmee, E. R.; Tan, Q.; Yang, C.-m.; Lins, A. R. Patent WO 2007/136577 A2, 2007. (g) Malhotra, B.; Gandelman, K.; Sachse, R.; Wood, N.; Michel, M. C. *Curr. Med. Chem.* **2009**, *16*, 4481−4489. (h) Hu, Q. Z.; Yin, L. N.; Jagusch, C.; Hille, U. E.; Hartmann, R. W. *J. Med. Chem.* **2010**, *53*, 5049−5053. (i) Pathak, T. P.; Gligorich, K. M.; Welm, B. E.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 7870−7871.

(2) For 1,1-diarylethanes, see: (a) Alami, M.; Messaoudi, S.; Hamze, A.; Provot, O.; Brion, J.-D.; Liu, J.-M.; Bignon, J.; Bakala, J. Patent WO 2009/147217 A1, 2009. (b) Cheltsov, A. V.; Aoyagi, M.; Aleshin, A.; Yu, E. C.-W.; Gilliland, T.; Zhai, D.; Bobkov, A. A.; Reed, J. C.; Liddington, R. C.; Abagyan, R. *J. Med. Chem.* **2010**, *53*, 3899−3906. (c) Chubb, N. A. L.; Cox, M. R.; Dauvergne, J. S.; Ewin, R. A.; Lauret, C. U.S. Patent 0,167,506, 2007. (d) Moree, W. J.; Li, B.-F.; Jovic, F.; Coon, T.; Yu, J.; Gross, R. S.; Tucci, F.; Marinkovic, D.; Zamani-Kord, S.; Malany, S.; Bradbury, M. J.; Hermandez, L. M.; O'Brien, Z.; Wen, J.; Wang, H.; Hoare, S. R. J.; Petroski, R. E.; Sacaan, A.; Madan, A.; Crowe, P. D.; Beaton, G. *J. Med. Chem.* **2009**, *52*, 5307−5310. (e) Beaton, G.; Moree, W. J.; Jovic, F.; Coon, T.; Yu, J. U.S. Patent 2006/0014797 A1, 2006. (f) Pathak, T. P.; Osiak, J. G.; Vaden, R. M.; Welm, B. E.; Sigman, M. S. *Tetrahedron* **2012**, *68*, 5203−5208. (g) Messaoudi, S.; Hamze, A.; Provot, O.; Tréguier, B.; Rodrigo De Losada, J.; Bignon, J.; Liu, J.-M.; Wdzieczak-Bakala, J.; Thoret, S.; Dubois, J.; Brion, J.-D.; Alami, M. *ChemMedChem* **2011**, *6*, 488−497.

(3) For leading references on the cross-coupling strategy, see: With catalyst/ligand control of chirality: (a) Do, H.-Q.; Chandrashekar, E. R. R.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 16288−16291. With enantioenriched substrates: (b) Hatanaka, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1990**, *112*, 7793−7794. (c) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024−5025. (d) López-Pérez, A.; Adrio, J.; Carretero, J. C. *Org. Lett.* **2009**, *11*, 5514−5517. (e) Taylor, B. L. H.; Swift, E. C.; Waetzig, J. D.; Jarvo, E. R. *J. Am. Chem. Soc.* **2011**, *133*, 389−391. (f) Greene, M. A.; Yonova, I. M.; Williams, F. J.; Jarvo, E. R. *Org. Lett.* **2012**, *14*, 4293−4296. (g) Taylor, B. L. H.; Harris, M. R.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 7790−7793. (h) Wisniewska, H. M.; Swift, E. C.; Jarvo, E. R. *J. Am. Chem. Soc.* **2013**, *135*, 9083−9090. (i) Maity, P.; Shacklady-McAtee, D. M.; Yap, G. P. A.; Sirianni, E. R.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 280−285. (j) Zhou, D.; Srinivas, H. D.; Dasgupta, S.; Watson, M. P. *J. Am. Chem. Soc.* **2013**, *135*, 3307−3310. (k) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2013**, *3*, 894−899. (l) Yonova, I. M.; Johnson, A. G.; Osborne, C. A.; Moore, C. E.; Morrissette, N. S.; Jarvo, E. R. *Angew. Chem., Int. Ed.* **2014**, *53*, 2422−2427. Strategies forming hetero analogues: (m) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191−13193. (n) Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738−20741.

(4) For leading reviews/highlights on asymmetric hydrogenation of terminal diarylalkenes, see: (a) Besset, T.; Gramage-Doria, R.; Reek, J. N. H. *Angew. Chem., Int. Ed.* **2013**, *52*, 8795−8797. (b) Pàmies, O.; Andersson, P. G.; Diéguez, M. *Chem.—Eur. J.* **2010**, *16*, 14232−14240. For representative leading references, see: (c) Mazuela, J.; Verendel, J. J.; Coll, M.; Schäffner, B.; Börner, A.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 12344−12353. (d) Mazuela, J.; Norrby, P.-O.; Andersson, P. G.; Pàmies, O.; Diéguez, M. *J. Am. Chem. Soc.* **2009**, *131*, 13634−13645. (e) Wang, X.; Guram, A.; Caille, S.; Hu, J.; Preston, J. P.; Ronk, M.; Walker, S. *Org. Lett.* **2011**, *13*, 1881−1883. (f) Bess, E. N.; Sigman, M. S. *Org. Lett.* **2013**, *15*, 646−649. (g) Caille, S.; Crockett, R.; Ranganathan, K.; Wang, X.; Woo, J. C. S.; Walker, S. D. *J. Org. Chem.* **2011**, *76*, 5198−5206. (h) Song, S.; Zhu, S.-F.; Yu, Y.-B.; Zhou, Q.-L. *Angew. Chem., Int. Ed.* **2013**, *52*, 1556−1559.

(5) Various other methods are known, such as oxyarylation of styrenes reported by Sigman and co-workers (see ref 1i). For other leading references, see: (a) Prat, L.; Dupas, G.; Duflos, J.; Queguiner, G.; Bourguignon, J.; Levacher, V. *Tetrahedron Lett.* **2001**, *42*, 4515−4518. (b) Bolshan, Y.; Chen, C.-y.; Chilenski, J. R.; Gosselin, F.; Mathre, D. J.; O'Shea, P. D.; Roy, A.; Tillyer, R. D. *Org. Lett.* **2004**, *6*, 111−114. (c) Okamoto, K.; Nishibayashi, Y.; Uemura, S.; Toshimitsu, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3588−3591. (d) Paquin, J.-F.; Defieber, C.; Stephenson, C. R. J.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 10850−10851. (e) Lewis, C. A.; Chiu, A.; Kubryk, M.; Balsells, J.; Pollard, D.; Esser, C. K.; Murry, J.; Reamer, R. A.; Hansen, K. B.; Miller, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 16454−16455.

(f) Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron* **2006**, *62*, 1833−1844. (g) Fessard, T. C.; Andrews, S. P.; Motoyoshi, H.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 9331−9334. (h) Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096−17098. (i) Podhajsky, S. M.; Iwai, Y.; Cook-Sneathen, A.; Sigman, M. S. *Tetrahedron* **2011**, *67*, 4435−4441. (j) Luan, Y.; Schaus, S. E. *J. Am. Chem. Soc.* **2012**, *134*, 19965−19968.

(6) For leading reviews of asymmetric transfer hydrogenation, see: (a) Ouellet, S. G.; Walji, A. M.; Macmillan, D. W. C. *Acc. Chem. Res.* **2007**, *40*, 1327−1339. (b) You, S.-L. *Chem.—Asian J.* **2007**, *2*, 820−827. (c) de Vries, J. G.; Mršić, N. *Catal. Sci. Technol.* **2011**, *1*, 727−735. (d) Zheng, C.; You, S.-L. *Chem. Soc. Rev.* **2012**, *41*, 2498−2518. (e) Rueping, M.; Sugiono, E.; Schoepke, F. R. *Synlett* **2010**, 852−865. For pioneering studies of organocatalytic asymmetric transfer hydrogenation, see: (f) Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32−33. (g) Yang, J. W.; Fonseca, M. T. H.; List, B. *Angew. Chem., Int. Ed.* **2004**, *43*, 6660−6662. For various subsequent reports on ATH in this field (>50 papers), mostly employing different imines, carbonyls, or their conjugated forms as substrates or intermediates, see the reviews in ref 6a−e. For selected relevant examples, see: (h) Martin, N. J. A.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13368−13369. (i) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498−7499. (j) Martin, N. J. A.; Ozores, L.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 8976−8977. (k) Martin, N. J. A.; Cheng, X.; List, B. *J. Am. Chem. Soc.* **2008**, *130*, 13862−13863.

(7) For a review of substrate-directable reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370. For a leading example of the use of a hydroxyl directing group in chiral acid catalysis, see: Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070−13071.

(8) For recent reviews of chiral phosphoric acid catalysis, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744−5758. (b) Terada, M. *Chem. Commun.* **2008**, 4097−4112. (c) Adair, G.; Mukherjee, S.; List, B. *Aldrichimica Acta* **2008**, *41*, 31−39. (d) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190−2201. (e) Kampen, D.; Reisinger, C. M.; List, B. *Top. Curr. Chem.* **2010**, *291*, 395−456. (f) Terada, M. *Synthesis* **2010**, 1929−1982. (g) Yu, J.; Shi, F.; Gong, L. *Acc. Chem. Res.* **2011**, *44*, 1156−1171. (h) Rueping, M.; Kuenkel, A.; Atodiresei, I. *Chem. Soc. Rev.* **2011**, *40*, 4539−4549. (i) Čorić, I.; Vellalath, S.; Müller, S.; Cheng, X.; List, B. *Top. Organomet. Chem.* **2013**, *44*, 165−194. For examples of our recent efforts in this area, see: (j) Chen, Z.; Wang, B.; Wang, Z.; Zhu, G.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 2027−2031. (k) Wang, Z.; Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6685−6688. (l) Chen, Z.; Sun, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13593−13596.

(9) See the Supporting Information for details.

(10) For reviews of indole in natural products and bioactive molecules, see: (a) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (b) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489−4497.

(11) Benzothiazoline **6** was first introduced by Akiyama for asymmetric transfer hydrogenation reactions. See: (a) Zhu, C.; Akiyama, T. *Org. Lett.* **2009**, *11*, 4180−4183. (b) Sakamoto, T.; Mori, K.; Akiyama, T. *Org. Lett.* **2012**, *14*, 3312−3315.

(12) There are a few approaches to access indole-substituted 1,1-diarylalkanes (e.g., ref 1i), but they are not applicable to 1,1-diarylethanes.

(13) *o*-QMs are important species in organic synthesis. For reviews, see: (a) Van De Water, R. W.; Pettus, T. R. R. *Tetrahedron* **2002**, *58*, 5367−5405. (b) Pathak, T. P.; Sigman, M. S. *J. Org. Chem.* **2011**, *76*, 9210−9215. (c) Willis, N. J.; Bray, C. D. *Chem.—Eur. J.* **2012**, *18*, 9160−9173. For leading examples of catalytic asymmetric reactions of *o*-QMs, see ref 1i and: (d) Jensen, K. H.; Pathak, T. P.; Zhang, Y.; Sigman, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 17074−17075. (e) Jensen, K. H.; Webb, J. D.; Sigman, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 17471−17482. (f) Jana, R.; Pathak, T. P.; Jensen, K. H.; Sigman, M. S. *Org. Lett.* **2012**, *14*, 4074−4077. During the revision of this manuscript, additional examples appeared. See: (g) El-Sepelgy, O.; Haseloff, S.; Alamsetti, S. K.; Schneider, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 7923−7927. (h) Hsiao, C.-C.; Liao, H.-H.; Rueping, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 13258−13263. It is worth mentioning that all of these examples invole *β-monosubstituted o*-QMs. Asymmetric reactions with *β,β-disubstituted o*-QMs remain challenging, and our reaction represents an early example.

(14) A similar interaction has also been proposed before. See: Simón, L.; Goodman, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 8741−8747.

(15) Regarding the enantioselectivity drop with 1-naphthyl substitution (**3m′** in Scheme 2), a plausible explanation is as follows. The naphthyl substituent further extends the conjugation of the *o*-QM intermediate. As a result, the charge density in the *o*-QM is more delocalized, which reduces the intermolecular interaction between the *o*-QM and HA*, thereby diminishing the enantiomeric discrimination.

(16) In a parallel study in our lab, the asymmetric substitution of such tertiary alcohols by indoles was achieved. See: Zhao, W.; Wang, Z.; Chu, B.; Sun, J. *Angew. Chem., Int. Ed.* **2014**, DOI: 10.1002/anie.201405252.

(17) We are aware of only one report on catalytic asymmetric reactions of *p*-QMs with high enantioselectivity, which deals with *δ-monosubstituted p*-QMs. See: Chu, W.-D.; Zhang, L.-F.; Bao, X.; Zhao, X.-H.; Zeng, C.; Du, J.-Y.; Zhang, G.-B.; Wang, F.-X.; Ma, X.-Y.; Fan, C.-A. *Angew. Chem., Int. Ed.* **2013**, *52*, 9229−9233. Examples involving *δ,δ-disubstituted p*-QMs are essentially unknown.

(18) For selected reviews and reports on the utility of 1,1,1-triarylalkanes, see: (a) Shchepinov, M. S.; Korshun, V. A. *Chem. Soc. Rev.* **2003**, *32*, 170−180. (b) Nair, V.; Thomas, S.; Mathew, S. C.; Abhilash, K. G. *Tetrahedron* **2006**, *62*, 6731−6747. (c) Palchaudhuri, R.; Nesterenko, V.; Hergenrother, P. J. *J. Am. Chem. Soc.* **2008**, *130*, 10274−10281. (d) Parai, M. K.; Panda, G.; Chaturvedi, V.; Manju, Y. K.; Sinha, S. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 289−292.

(19) For recent reviews of the formation of all-carbon quaternary stereocenters, see: (a) Das, J. P.; Marek, I. *Chem. Commun.* **2011**, *47*, 4593−4623. (b) Hawner, C.; Alexakis, A. *Chem. Commun.* **2010**, *46*, 7295−7306.

(20) Terada and co-workers pioneered asymmetric nucleophilic addition to 3-vinylindoles to form indol-3-yl tertiary stereocenters. See: Terada, M.; Moriya, K.; Kanomata, K.; Sorimachi, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 12586−12590.

(21) We also evaluated the cytotoxicity of **3m** in certain types of normal mammalian cells and found that **3m** is more active in the cancer cells. See the Supporting Information for more details.