Organic LETTERS

Letter

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# Friedel–Crafts Alkylation of Indoles with *p*-Quinols: The Role of Hydrogen Bonding of Water for the Desymmetrization of the Cyclohexadienone System

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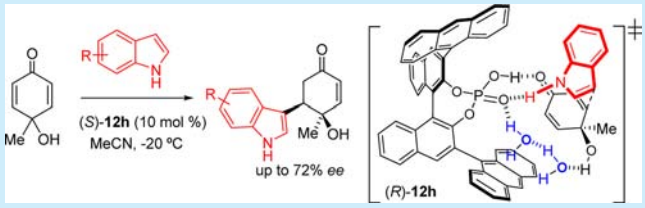
Supporting Information

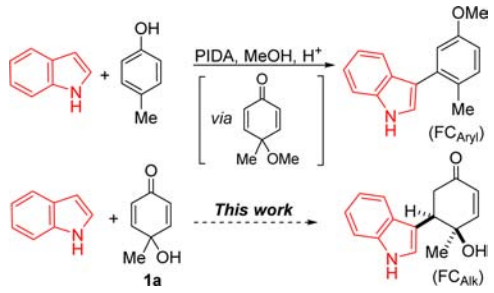
**ABSTRACT:** Lewis acid catalyzed Friedel–Crafts alkylation of indoles has been achieved in high yields and selectivities using *p*-quinols as electrophiles. (*S*)-Binol-3,3′-(9-anthracenyl)-phosphoric acid was able to catalyze the enantioselective formation of 5-(3-indole)-2-cyclohexenone derivatives. Experimental results and theoretical calculations explained the enantioselectivity based on a transition state where two water molecules act as a tether joining the *p*-quinol with the phosphoric acid and the NH of indole, thus facilitating the desymmetrization of the prochiral cyclohexadienone framework.




The chemistry of indoles has been extensively studied due to the widespread appearance of these units in a number of structures ranging from natural products[1] to pharmaceutical compounds.[2] Different approaches have been reported for the synthesis of the heterocyclic system and its functionalization.[3] 3-Substituted indoles, the most frequently present moieties in such structures, are available by Friedel–Crafts (FC) reactions. The development of efficient asymmetric versions of these alkylations has been the focus of interest of several groups in the past decades.[4] Lewis acids incorporating chiral ligands, chiral Brønsted acids, and organocatalysts are currently available to access optically active electrophilic aromatic substitution products.[5] Alkylation of indoles with enones,[6] *β*,*γ*-unsaturated-*α*-keto esters,[7] or nitroalkenes[8] is a powerful C–C bond forming process giving the 1,4-addition products that have also been achieved using asymmetric catalysts. Alkylidene malonates,[9] *α*′-hydroxy-*α*,*β*-unsaturated ketones,[10] and *α*′-phosphoric enones[11] are also useful electrophiles for alkylation of indoles.

4-Hydroxy-4-alkyl-2,5-cyclohexadienones (*p*-quinol derivatives) are double Michael-type acceptors[12] with a challenging prochiral cyclohexadienone moiety. Catalytic desymmetrization of such moieties has been mainly achieved in an intramolecular fashion via Heck,[13] Stetter,[14] and Michael type reactions.[15,16] The intermolecular catalytic desymmetrization of *p*-quinols has been accomplished by Feringa et al. in the Cu-catalyzed conjugate addition of dialkylzinc reagents, using enantiopure phosphoramidite ligand.[17] Despite the interest in FC alkylations ($FC_{Alk}$) of indoles in organic chemistry, the reaction using *p*-quinols as alkylating agents remained unexplored to date. A related FC arylation ($FC_{Aryl}$) reaction has been reported by reaction of *p*-cresol and indole in the presence of (diacetoxyiodo)benzene (PIDA), which in situ generated the 4-methoxy-4-methyl-2,5-cyclohexadienone moiety. 3-(5-Methoxy-2-methyl phenyl)-1*H*-indole was formed as a result of the aromatization of the initial 1,4-addition product (Scheme 1).[18]

**Scheme 1. FC Reactions of Indole with *p*-Quinol Systems**




In continuation of our work devoted to extending the synthetic applications of *p*-quinols,[19] we present herein the intermolecular FC reaction of indoles using *p*-quinols as electrophilic alkylating agents, to give the desired 1,4-addition products under mild conditions in a highly diastereoselective manner. We also report our attempts to achieve an enantioselective version of the process and a computational study to rationalize the experimental observations (Scheme 1).

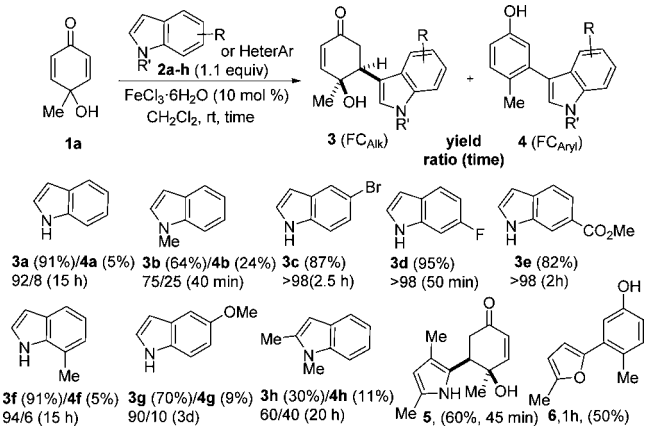
**Received:** March 24, 2016
**Published:** April 18, 2016





DOI: 10.1021/acs.orglett.6b00781
*Org. Lett.* 2016, 18, 2224–2227

**Scheme 2. Iron Catalyzed FC Reaction with *p*-Quinol 1a**



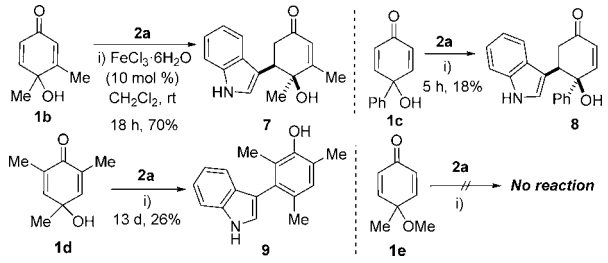

We initiated our study using *p*-quinol **1a**[19a] and 1*H*-indole **2a** as model substrates (Scheme 2). After extensive screening with different catalysts, solvents, and temperatures,[20] we could establish that the best results were obtained using $FeCl_3{\cdot}6H_2O$ (10 mol %) and $CH_2Cl_2$ (0.1 M) as solvent at rt. Under these conditions, a mixture of **3a** and **4a** was obtained in a 92:8 ratio (GC/MS), from which **3a** was isolated in 91% yield as a single diastereomer.[21] Compound **3a** resulted from the 1,4-addition of indole to **1a** from the less hindered face, containing the hydroxyl.[22] Formation of **4a** must result from OH elimination and enolization of **3a**, favored by the acidic conditions. We next evaluated different substituted indoles under the optimized conditions (Scheme 2). N-Me indole **2b** reacted faster than **2a**, giving a 75:25 mixture of **3b** (64%) and **4b** (24%). 5-Bromo indole **2c**, 6-fluoro indole **2d**, and 6-methoxycarbonyl indole **2e** gave only the $FC_{Alk}$ products **3c**, **3d**, and **3e** (87%, 95%, and 82% yield). Indoles having an electron-donating group, such as 7-methyl and 6-methoxy **2f** and **2g**, gave the $FC_{Alk}$ products **3f** and **3g** as major products, although variable amounts of aromatic derivatives **4f** and **4g** were also formed. A lower yield was observed in the reaction of **1a** with 1,2-dimethylindole, probably due to the steric hindrance at the C-3 position.

Other electron-poor systems, such as N-Boc indole as well as 5-nitro and 4-carboxaldehyde 1*H*-indoles, did not react after long reaction times and upon heating (60 °C). Other electron-rich heterocycles were also checked as substrates for alkylation with *p*-quinol **1a**. No evolution was observed with furan, thiophene, and 2-methylthiophene. Pyrrole gave a complex mixture where the 2-pyrrole substituted monoalkylation product and the 2,5-dialkylated pyrrole derivatives were detected in a 1:3 ratio respectively (see compounds **10** and **11** in the Supporting Information).[23] 2,4-Dimethyl pyrrole gave the $FC_{Alk}$ product **5** (60% yield), whereas only the $FC_{Aryl}$ derivative **6** (50% yield) was formed in the reaction with 2-methyl furan (Scheme 2).

Other *p*-quinols, such 3-methyl-*p*-quinol **1b**, reacted with **2a** to give the $FC_{alk}$ product **7** in 70% yield, resulting from the attack of **2a** to the unsubstituted *β*-carbon of the precursor. 4-Phenyl-*p*-quinol **1c** gave compound **8** in a low 18% yield. 2,6-Dimethyl-*p*-quinol **1d** proved to be a poor Michael acceptor, and the reaction gave the $FC_{Aryl}$ derivative **9** in 26% yield. Interestingly, no reaction occurred with *p*-quinol methyl ether **1e**, showing that under these conditions the free OH is crucial in the FC process (Scheme 3).

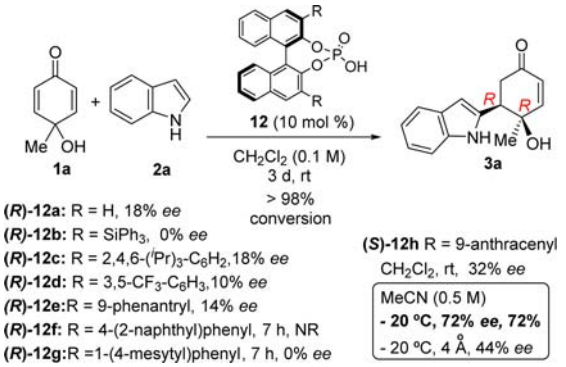
The great interest in the alkylation products for further transformations prompted us to explore the enantioselective version of this FC process. Reaction between **1a** and **2a** was chosen as a model to study the desymmetrization of the prochiral

**Scheme 3. Iron Catalyzed FC Reaction of 2a with 1b−e**




2,5-cyclohexadienone moiety. Initially, we tried iron chiral catalysts[24] generated from $FeCl_3{\cdot}6H_2O$ and enantiopure ligands such as Evan's bis(oxazolines), Feringa's phosphoramidites,[17] (*R*)-VAPOL, or chiral iron Lewis acids derived from Salen derivatives,[24] but we did not observed enantioselection. Use of the (*S*)-Phanephos ligand gave **3a** in 8% *ee* and low conversion (20%). Based on previous asymmetric Brønsted acid catalyzed indole alkylations,[25] we checked the model reaction in the presence of (*R*)-BINOL derived phosphoric acids **12** (Scheme 4).

**Scheme 4. Enantioselective FC of 2a with *p*-Quinol**[a]




[a]HPLC (Chiralpack IC-0.8 mL/min-15% $^i$PrOH).

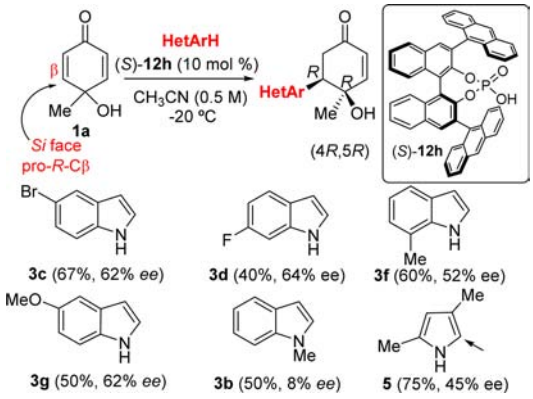
Reaction with (*R*)-**12a−e** (10 mol %) gave the $FC_{Alk}$ **3a** in a >98% conversion on the basis of GC-MS analysis, but unfortunately with null or poor enantiomeric excess. No reaction was observed with 4-(2-naphthyl)phenyl phosphoric acid **12f**, while a poor conversion (12%) and 0% *ee* resulted in the presence of 1-(4-mesytyl)phenyl substituted **12g**. The best result in terms of conversion and enantioselectivity (>98%, 32% *ee*) was obtained using 9-anthracenyl phosphoric acid (*S*)-**12h**. Final tuning[23] of other parameters such as solvents, substrate concentration, temperature, additives,[26] and catalyst loading allowed the best conditions to be established [(*S*)-**12h** (10 mol %), $CH_3CN$ (0.5 M), −20 °C] to obtain **3a** in a 72% yield and 72% *ee*. Interestingly, the addition of 4 Å molecular sieves to the reaction significantly decreased both the rate and enantioselectivity (17%, 10 d, 44% *ee*). This indicated the important role of water in the catalytic process.[27] The (4*R*,5*R*) absolute configuration of the major enantiomer **3a** was established by comparison of the experimental ECD spectra of pure enantiomers (separated by chiral-HPLC from an enantioenriched mixture).[23]

We next explored the scope of the (*S*)-**12h** catalyzed FC reaction varying the heterocycle substitution under the optimized reaction conditions (Scheme 5). Electron-withdrawing substituted indoles, such as 5-bromo or 6-fluoro indole **2c** and **2d** gave the $FC_{alk}$ products **3c** and **3d** in moderate to good yields and 62% *ee* and 64% *ee*. No significant differences were observed in the



DOI: 10.1021/acs.orglett.6b00781
*Org. Lett.* 2016, 18, 2224−2227

**Scheme 5. Scope of the Enantioselective FC Alkylation**




reactivity of electron-rich indoles **2f** and **2g**, since the reactions were completed in 6 days leading to **3f** and **3g** in 52% *ee* and 62% *ee*, respectively. 2,4-Dimethyl pyrrole reacted faster (24 h) affording compound **5** in 45% *ee* (75% yield). In all cases the $FC_{aryl}$ product **4** was not observed. Methyl 1*H*-indole-6-carboxylate did not react under the standard conditions. N-Me indole gave the $FC_{alk}$ compound **3b** in a 50% yield, but with only an 8% *ee*, thus indicating the essential role of the NH in the process. The presence of the free OH in the *p*-quinol was also crucial for the reactivity, since using 4-methoxy-*p*-quinol derivative **1e** gave no reaction.

To confirm the interactions responsible for the enantioselectivity, we developed a computational study of the bond forming step taking into account three important experimental observations: (1) the lack of reaction of indole **2a** with 4-methoxy-*p*-quinol **1e**, lacking the free OH; (2) the important role of traces of water for both reactivity and enantioselectivity; and (3) the differences in enantioselectivity for the NH free indole (72% *ee*) and the *N*-methylindole (8% *ee*). Our DFT investigations were carried out using as a model system the reaction of **1a** and **2a** catalyzed by the (*R*) enantiomer of **12h** leading to the desymmetrization product. The two-point coordination Akiyama model,[28] described for coordination of the BINOL phosphoric acid catalyst to the two reagents, was adopted. To reproduce the experimentally observed role of water in the FC reaction, two molecules of $H_2O$ were included in our studies. In the absence of indole, the water H-bonding-coordinated system was positioned (in a linear-*trans* mode) in a network that also involves the hydroxyl group of *p*-quinol **1a** and the basic site of (*R*)-binol-3,3′-(9-anthracenyl)-phosphoric acid **12h** (Figure 1A). In order to conveniently carry out the DFT study,[23] we selected the reaction on the less hindered face (OH containing face of the *p*-quinol), as this was experimentally observed. The approach to the rear face of *p*-quinol in the **1a**-2·$H_2O$-(*R*)-**12h** associated system is blocked by steric interference of the methyl group. In contrast, the coordination of $H_2O$ opens a cavity in the OH-containing face that can be later occupied by indole **2a**. Without disturbing the water-mediated H-bonding network, indole N−H also binds the phosphoric acid basic site. The most stable transition state was calculated to be the one resulting from the *Si*-face, pro-*R* *β*-carbon attack, shown in Figure 1B, leading to the (4*S*,5*S*)-**3a** enantiomer.

Interestingly, it was found that the presence of water not only forms a more compact cavity in (4*S*,5*S*)-$H_2O$-$\mathbf{TS}_{I-II}$ (H−O distances 1.76, 1.72, and 1.77 Å) than in the diastereomeric one (approach to the pro-*S* *β*-carbon) but also plays a stabilizing role in this TS, through an OH−*π* interaction with the aryl ring of the phosphoric acid.[30] Moreover, a comprehensive analysis of both

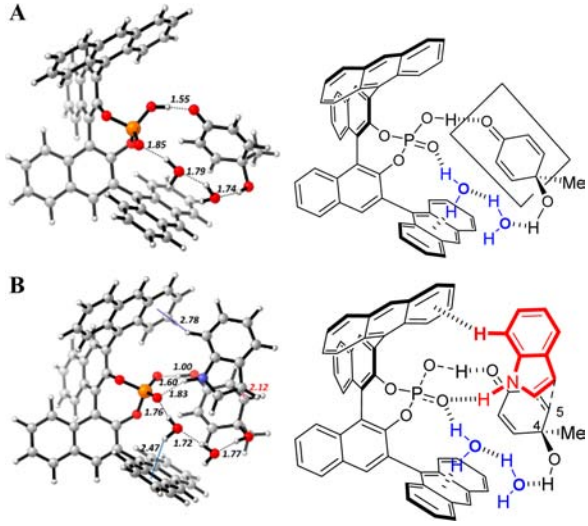



**Figure 1.** Calculated complexes of (A) **1a**-(*R*)-**12h**-2·$H_2O$ complex and (B) (4*S*,5*S*)-$H_2O$-$\mathbf{TS}_{I-II}$. Relevant atom distances (Å) are shown (wB97XD/PCM($CH_3CN$)/6-31G*//wB97XD/6-31G*).[29]

transition structures revealed that the lowest-energy transition state represented in Figure 1B exhibited another important noncovalent interaction, namely an edge-to-face *π*−*π* interaction (2.78 Å) between the indole (H-7) and an aryl ring of the catalyst. This type of interaction has been recognized to play important roles in chemical and biological recognition processes,[31] and also in the enantioselectivity, as shown by the desymmetrization of **1a**. In order to estimate the effect of the water molecules in the reaction, both the nonassisted and the water-assisted variants of the *Re* face, pro-*S* approach have been computed.[23] Comparison of the energies of activation (in gas phase) and the structures of the transition states of the FC reaction indicated that the network of water molecules favored (by 9 kcal/mol) the 1,4-addition of **2a** to **1a**. This effect might be due to the modulation of the acidity of phosphoric acid (*R*)-**12h**, which translates into an increase of the nucleophilicity of indole at its $C_3$ position. In agreement with these calculations, the desymmetrization of **1a** in the (*R*)-**12h** catalyzed reaction with **2a** must occur preferentially by the *Re*-face, pro-*S* *β*-carbon double bond of **1a** to give the (4*S*,5*S*)-**3a**. Thus, the (4*R*,5*R*)-**3a** enantiomer must be formed in the (*S*)-**12h** catalyzed process, as experimentally observed.

In summary, we have developed an efficient method for the construction of 5-indolyl substituted-4-hydroxy-4-methyl-2-cyclohexenone systems in a high *π*-facial diastereoselective manner. We demonstrated for the first time that intermolecular FC alkylations of indoles can be achieved using *p*-quinols as an electrophilic partner. The asymmetric version of the process has been accomplished in the presence of chiral BINOL derived phosphoric acids as organocatalysts with up to 72% *ee*. The computational study of the asymmetric FC reaction confirmed the important role of water, increasing the nucleophilicity of the $C_3$ position of indole, as well as the origin of stereoselectiviy based on *π*-stacking (*π*−*π* and HO−*π*) and steric interactions.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00781.

Computational studies (PDF)



DOI: 10.1021/acs.orglett.6b00781
*Org. Lett.* 2016, 18, 2224−2227

Experimental procedures, spectroscopic data, and copies of $^{1}H$ and $^{13}C$ NMR spectra for all new compounds (PDF)
Crystallographic data (CIF)

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work is dedicated to Prof. Ángel Rodríguez de Lera on the occasion of his 60th birthday. We thank MICINN (Grants CTQ2011-24783, CTQ2012-37734-C02-01, and CTQ2014-53894-R) for financial support. C.G.G. and L.O.R. thank MEC for FPU and FPI fellowships. We thank *Centro de Supercomputación de Galicia* (CESGA) for the generous allocation of computing resources.

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(20) No reaction took place without a Lewis acid catalyst. Catalysts surveyed: $FeCl_3$, $Fe(OTf)_3$, $Cu(OTf)_2$, and *p*-TsOH. Solvents: $CH_3CN$, AcOEt, $CHCl_3$, $CH_2Cl_2$, or DCE. Temperature: rt or 0 °C.
(21) Structural assignment was confirmed by X-ray diffraction of **3c** CCDC 1457374: *Mr* $C_{15}H_{14}BrNO_2{\cdot}CHCl_3$. Unit Cell Parameters: *a* 7.50910(10) Å; *b* 10.1225(2) Å; *c* 12.5419(2) Å. Space group $P\bar{1}$.
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(26) Binary acid catalysis were also evaluated, by combining Brønsted acid (*S*)-**12h** with Lewis acids, but a low *ee* resulted; see Supporting Information for details.
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## NOTE ADDED AFTER ASAP PUBLICATION

The toc/abstract graphic was corrected on April 19, 2016. On May 6, 2016, a missing assignment of the configuration of the catalyst **12h** and a mistake in the configuration of compounds in the Supporting Information were corrected.



DOI: 10.1021/acs.orglett.6b00781
*Org. Lett.* 2016, 18, 2224−2227