COMMUNICATION

Enantioselective Friedel-Crafts Reaction of Hydroxyarenes with Nitroenynes to Access Chiral Heterocycles *via* Sequential Catalysis

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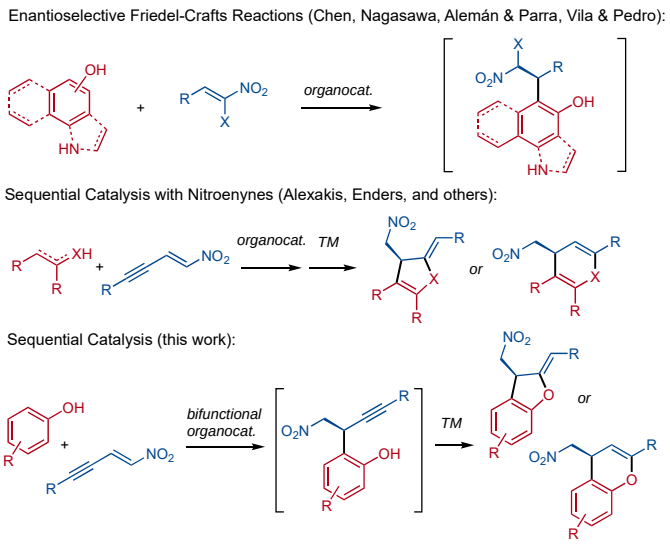
Naphthols, hydroxyindoles and an activated phenol are reacted with differently substituted (*E*)-nitrobut-1-en-3-ynes using the commercially available Rawal's chiral squaramide. The corresponding β-nitroalkynes were obtained with good yields and excellent enantioselectivities. Moreover, dihydronaphthofurans can be accessed *via* silver catalysed cyclization in a tandem one-pot procedure, with high preservation of the optical purity.

The enantioselective addition of nucleophilic aromatic compounds in a Friedel-Crafts fashion has been of interest for several decades.[1] While more reactive indoles and pyrroles focused the attention at the early stages,[2] challenging hydroxyarenes, such as naphthols and phenols, were successfully engaged in catalytic enantioselective reactions more recently. Nowadays, asymmetric methodologies exist for the addition of phenols and naphthols to ketones, acetals, aldehydes, imines, Michael-acceptors or allylic systems.[3,4] Among the catalytic systems described, bifunctional organocatalysts deserve a special mention.[5] These organic molecules are typically decorated with a H-bond donor, such as a (thio)urea or a squaramide, and a tertiary amine; and are based on readily accessible chiral scaffolds, typically cyclic diamines or *Cinchona* alkaloids. These systems are especially effective for the addition of hydroxyarenes to nitroalkenes. Chen and coworkers described in 2007 the addition of 2-naphthols to nitroalkenes catalysed by a thiourea derived from cinchonidine.[6a] Interestingly, the authors observed a dimeric hydroxylamine with extended reaction times. In 2010, Nagasawa introduced a new guanidine catalyst for a similar transformation using sesamol and 1- and 2-naphthol as nucleophiles.[6d] Parra, Alemán and coworkers described in 2013 the synthesis of *trans*-dihydroarylfurans by enantioselective addition of hydroxyarenes to 1-bromonitroalkenes, followed by cyclization.[6e] Bifunctional thioureas are also able to catalyse the intermolecular dearomatization of 2-naphthols with nitroethylene, as reported by the group of You in 2015.[6f] More recently, our group described the addition of hydroxyindoles to nitroalkenes, achieving excellent enantioselectivies. In this case, the activating effect of the hydroxyl group causes the reaction to take place in the carbocyclic ring, overcoming the more common substitution in the azole ring of indoles.[6g]



Scheme 1. Previous examples of F-C reactions between hydroxyarenes and nitroalkenes (top). Our application to the synthesis of chiral heterocycles via sequential catalysis (bottom).

On the other hand, the combination of a chiral organocatalyst and a transition metal (TM) in a sequential fashion is a powerful strategy for the construction of complex chiral scaffolds from simple starting materials.[7] In a seminal report, Jørgensen and coworkers described an enantioselective reaction between propargylmalonitriles and *N*-Boc imines.[8] This sequential process was catalysed by a chiral thiourea and a Au(I) complex. The activated C–H undergoes a Mannich-type reaction leading to the amino alkyne intermediate, which cyclises in a 5-*exo*-dig fashion, producing the corresponding dihydropyrrole after isomerization. The presence of an alkyne is a commonplace in sequential catalysis, especially those

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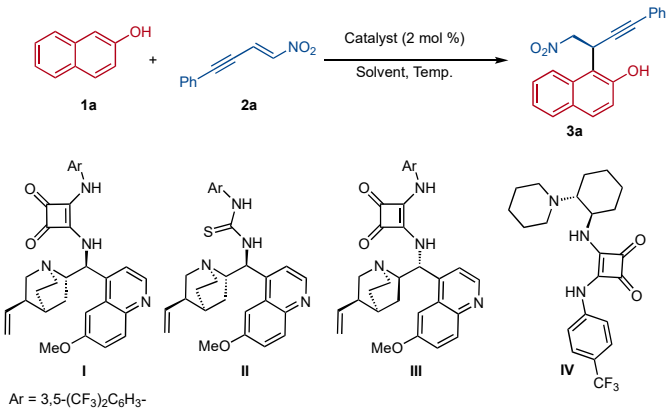
conjugated with an activated alkene. This strategy takes advantage of the well-developed organocatalysed conjugate addition,[9] followed by transition metal-catalysed cyclization.[10] The group of Enders exploited this approach using organocatalysts derived from *Cinchona* alkaloids and silver salts to prepare different chiral heterocyclic products.[11] Among the alkyne-containing electrophiles suitable for sequential catalysis, we focused our attention in nitroenynes **2** as electrophiles.[12,13] With these precedents in hand, we aimed at developing of an enantioselective method for the reaction of hydroxyarenes **1** with nitroenynes **2** by means of sequential catalysis, combining a chiral bifunctional organocatalyst with a transition metal. The planned strategy includes an organocatalysed Friedel-Crafts reaction of the hydroxyarene with the activated alkene, followed by cyclization of the hydroxyl group with the alkyne. This cyclization will be facilitated by the transition metal of choice, paying special attention to the compatibility between both catalytic systems.

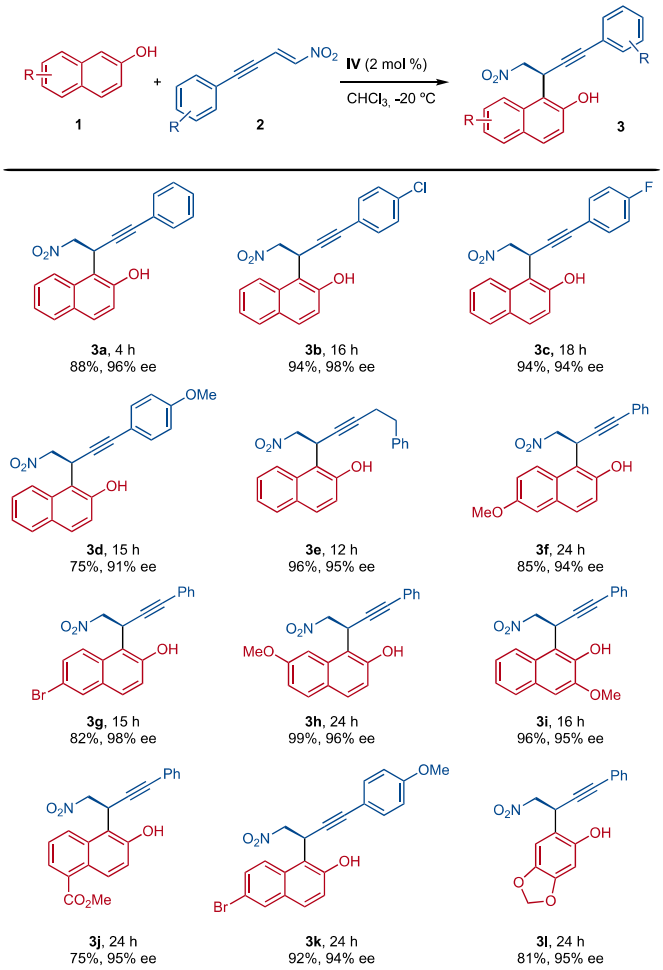
Table 1. Screening of the reaction conditions.[a]



Entry	Solvent	T (°C)	Cat.	t (h)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	25	**I**	2	86	71[d]
2	CH_2Cl_2	25	**II**	4	71	58[d]
3	CH_2Cl_2	25	**III**	4	42	83
4	CH_2Cl_2	25	**IV**	3	90	90
5	Toluene	25	**IV**	16	50	88
6	THF	25	**IV**	48	<10	nd
7	$CHCl_3$	25	**IV**	4	87	92
8	$CHCl_3$	0	**IV**	3	80	92
9	$CHCl_3$	−20	**IV**	4	88	96
10	$CHCl_3$	−40	**IV**	6	78	90

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), catalyst (2 mol%), solvent (1 mL).[b] Isolated yield after purification by column chromatography.[c] Enantiomeric excess determined by HPLC analysis. [d] Opposite enantiomer. nd: not determined. Absolute configuration in **3a** was established by analogy with reference [6g].

Our investigation started with the optimization process of the addition of 2-naphthol **1a** to nitroenyne **2a** with different bifunctional organocatalysts (Table 1). To our delight, quinine-derived squaramide **I** in dichloromethane delivered the desired product in excellent enantioselectivity, while an analogous thiourea **II** afforded notably diminished yield and enantioselectivity (Table 1, entries 1-2). The pseudo-enantiomeric squaramide **III**, derived from quinidine, afforded nitroalkyne **3a** in moderate yield and improved enantioselectivity (Table 1, entry 3). Simple and commercially available Rawal's squaramide[14] **IV** gave excellent yield and high enantioselectivity (Table 1, entry 4). Further screening on the role of solvent showed toluene maintains the enantioselectivity, although with a significant drop in reactivity, and more coordinating THF virtually shuts down reactivity (Table 1, entries 5-6). Chloroform gave slightly better results than dichloromethane (Table 1, entry 7). Temperature screening allowed us to improve the enantioselectivity to 96% ee, maintaining the reactivity, by performing the reaction at −20 °C (Table 1, entries 8-10).

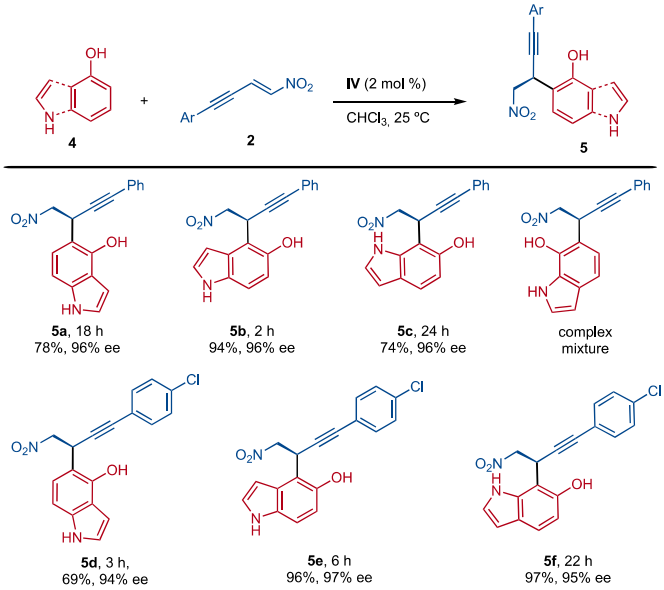


Scheme 2. Substrate scope of naphthols and phenol. Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), **IV** (2 mol%), $CHCl_3$ (1 mL) at −20 °C. Isolated yield after purification by column chromatography. Enantiomeric excess determined by HPLC analysis.

With the optimised reaction conditions in hand, we explored then the scope of the transformation (Scheme 2). First, differently substituted aromatic nitroenynes **2** were subjected to our methodology using 2-naphthol **1a**. We obtained the desired compounds **3** in high yields (75-94%) and with excellent enantioselectivities (91-98% ee), regardless of the electronic nature of the substituents in **2**. Gratifyingly, nitroenyne **2e**, with an aliphatic substituent, also delivered excellent results (96% yield and 94% ee). We next studied the scope using different 2-naphthols, also obtaining excellent

results. Finally, challenging sesamol **1l** was also amenable under our reaction conditions (81% yield, 95% ee).

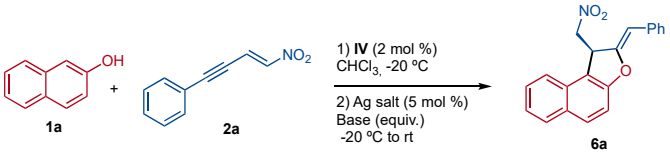
At this point, we planned to extend our methodology to hydroxyindoles **4** (Scheme 3). These aromatic compounds are very interesting substrates, as they allow for substitution in the carbocyclic ring of indoles even in the absence of substituent or protecting groups in the azole ring.[15] After a careful optimization process using 4-hydroxyindole **4a** and nitroenyne **1a**,[16] we found Rawal's squaramide was again the most effective organocatalyst, while chloroform was also chosen as the best solvent. Noteworthily, in this case, we observed formation of the C5-alkylated product, together with C7-alkylated and C5-C7-dialkylated side-products. Final reaction conditions afforded the desired C5-alkylated hydroxyindole **5a** in 78% yield and 96% ee, observing a 13:1:3 ratio of desired product, C7 regioisomer and dialkylated at C5 and C7. We continued by applying these conditions to regioisomeric hydroxyindoles. 5-Hydroxyindole **4b** reacted exclusively in the C4 position, delivering the desired product **5b** in 91% yield and 96% ee, while 6-hydroxyindole **4c** was alkylated in the C7, also in good yield and excellent enantiocontrol (74%, 96% ee). Unfortunately, engaging 7-hydroxyindole **4d** under our reaction conditions resulted in a complex mixture.[6g] Nitroenyne **2b** was also reacted with the three hydroxyindoles, giving the desired products in moderate to excellent yields and with excellent enantioselectivities (69-97%, 94-97% ee).



Scheme 3. Substrate scope of hydroxyindoles. Reaction conditions: **4** (0.15 mmol), **2** (0.1 mmol), **IV** (2 mol%), $CHCl_3$ (1 mL) at 25 °C. Isolated yield after purification by column chromatography. Enantiomeric excess determined by HPLC analysis.

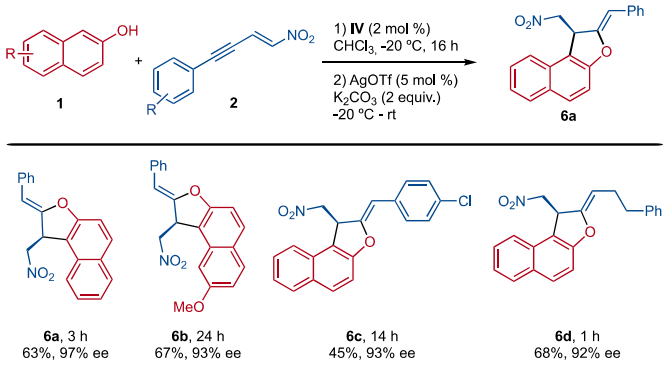
Having developed a solid method for the Friedel-Crafts reaction of different hydroxyarenes with nitroenynes **2**, we continued by developing a sequential catalytic process. We started by adding different silver salts, in combination with a base, to the reaction mixture upon completion of the Friedel-Crafts reaction. To our delight, just a 5 mol % of simple AgOTf and 2 equivalents of K_2CO_3 were sufficient to obtain a cyclised compound in 70% yield, preserving the optical purity (Table 2, entry 1). NMR experiments revealed the new species formed was the product of 5-*exo*-dig cyclisation, dihydronaphthofuran **6a**. We then tested different silver salts and bases, obtaining no conversion in most of the cases (Table 2, entries 2-5). Moreover, control experiments proved the importance of the amount of base (Table 2, entries 6-7). The sequential protocol to obtain these enantioenriched nitro-dihydronaphthofurans was extended to a small family of compounds, obtaining moderate to good yields and excellent preservation of the optical purity (Scheme 4). Unfortunately, the reaction conditions were ineffective with the substrates derived from hydroxyindole.

Table 2. Screening of the reaction conditions for the sequential process.[a]



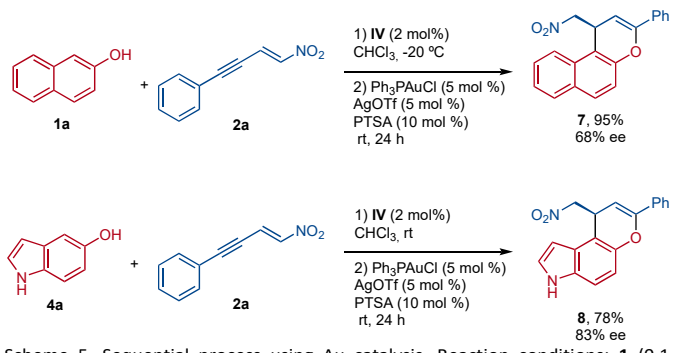
Entry	Ag salt	Base (equiv.)	t (h)	Yield (%)[b]	ee (%)[c]
1	AgOTf	K_2CO_3 (2)	3	70	97
2	AgOAc	K_2CO_3 (2)	16	nr	nd
3	Ag_2O	K_2CO_3 (2)	3	33	nd
4	AgOTf	Cs_2CO_3 (2)	16	nr	nd
5	AgOTf	Et_3N (2)	16	nr	nd
6	AgOTf	K_2CO_3 (1)	3	64	92
7	AgOTf	none	16	nr	nd

[a]Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), **IV** (2 mol%), $CHCl_3$ (1 mL) at −20 °C. Then, Ag salt and base were added and the reaction allowed to reach room temperature.[b] Isolated yield after purification by column chromatography.[c] Enantiomeric excess determined by HPLC analysis. nr: no cyclisation reaction. nd: not determined.



Scheme 4. Substrate scope of sequential process using Ag catalysis. Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), **IV** (2 mol%), $CHCl_3$ (1 mL) at −20 °C. Then, AgOTf (0.005 mmol) and K_2CO_3 (0.2 mmol) were added and the reaction allowed to reach room temperature Isolated yield after purification by column chromatography. Enantiomeric excess determined by HPLC analysis.

Finally, we also briefly explored the use of Au(I) catalysts in the sequential catalytic process (Scheme 5).[17] Interestingly, in this case we observed the formation of the 6-*endo*-dig cyclisation products **7**. However, the corresponding products were isolated in good yield but with variable erosion in the optical purity, for both derived from 2-naphthol or from 5-hydroxyindole.



Scheme 5. Sequential process using Au catalysis. Reaction conditions: **1** (0.1 mmol), **2** (0.12 mmol), **IV** (2 mol%), $CHCl_3$ (1 mL) at –20 °C. Then, Ph_3PAuCl (0.005 mmol), AgOTf (0.005 mmol), PTSA (0.01 mmol) were added and the reaction allowed to reach room temperature. Isolated yield after purification by column chromatography. Enantiomeric excess determined by HPLC analysis.

Conclusions

In summary, we have developed a method for the Friedel-Crafts reaction of hydroxyarenes, such as 2-naphthols, hydroxyindoles and an activated phenol, with differently substituted nitroenynes, including one with an aliphatic substituent. The desired products were obtained in good to excellent yields and with excellent regio- and enantioselectivities in all cases. Moreover, we applied this methodology to a sequential catalytic process in a one-pot procedure. Silver triflate and K_2CO_3 were effective for synthesis of optically enriched dihydronaphthofurans, with good yields and excellent preservation of the optical purity in this 2-step, one-pot protocol. Finally, a gold catalytic system was used to form the corresponding dihydropyranes in excellent yields, albeit with variable erosion in the optical purity.

Conflicts of interest

There are no conflicts to declare

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