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Enantioselective Friedel-Crafts alkylation of indole with nitroalkenes in the presence of bifunctional squaramide organocatalysts

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ABSTRACT

A series of chiral bifunctional quinine and 2-aminoDMAP based squaramide organocatalysts are evaluated in Friedel-Crafts alkylation of indoles with nitroolefins. These 3-substituted indole derivatives are synthesized in the presence of sterically encumbered *tert*-butyl squaramide/quinine with high enantioselectivity (up to >99% ee) and moderate chemical yields (up to 80%) by representing as chiral precursors for very important biologically active molecules. Besides, this asymmetric transformation provides a very simple, efficient, clean and environmental friendly route. In addition, this process has very mild reaction conditions such as ambient temperature and usage of only 2 mol% catalyst loading compared to previous studies in literature.

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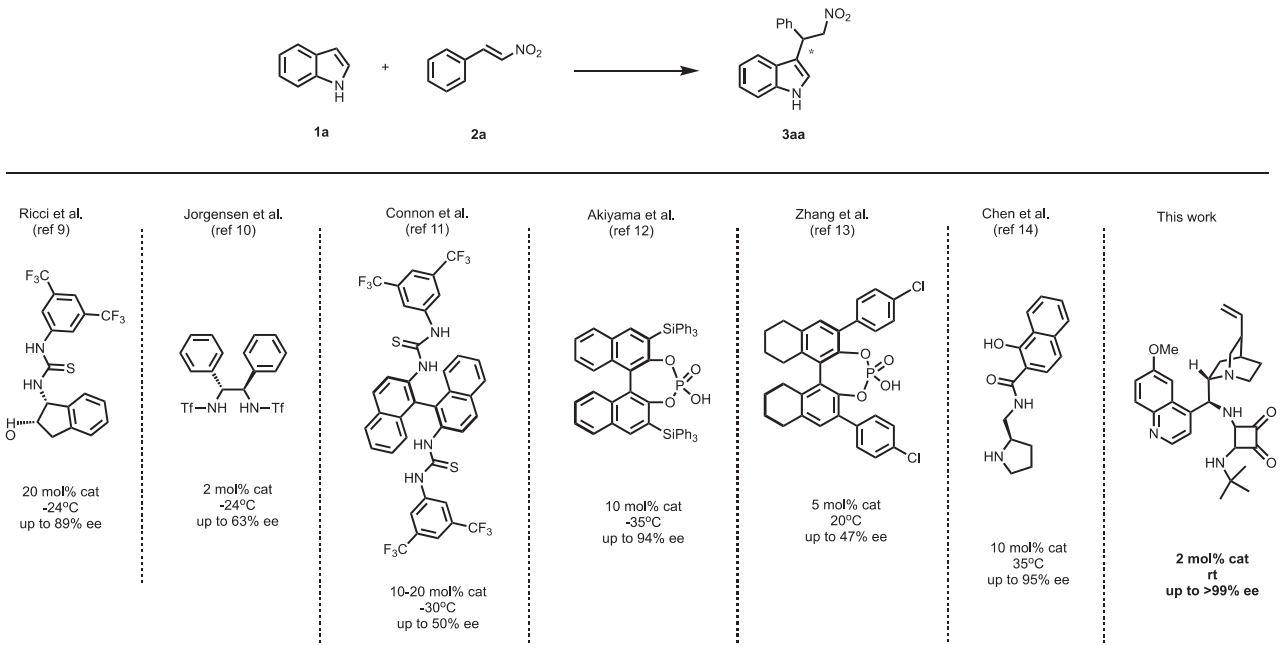
Introduction

The Friedel-Crafts alkylation is one of the most substantial reaction type to construct a new C—C bond in organic chemistry [1]. Due to indole's unique structure in pharmaceutical environment [2], and chemical diversity of nitro unit of nitroalkenes [3], these compounds are precious starting materials for many synthetic transformations. The Friedel-Crafts alkylation of indole with nitroalkenes is a key reaction in order to get 3-substituted indole derivatives which are useful intermediates for biologically active compounds such as tryptamines [4], and 1,2,3,4-tetrahydro-β-carbolines [5]. The asymmetric version of this reaction is catalyzed mostly by the combination of ligands and metal complexes [6], charged organocatalysts [7] and inorganic materials [8]. Moreover, the organocatalysis which environmental friendly side was tested firstly by Ricci [9] et al. in 2005 in the presence of a simple thiourea organocatalyst with the usage of 20 mol% and synthesized 3-substitued indole derivatives with high enantioselectivities (up to 89% ee) at −24 °C. In the same year, this asymmetric Friedel-Crafts alkylation reaction was catalyzed with H-bonding bis-sulfonamides by Jorgensen [10] and his co-workers. They reached up to only 63% ee in the presence of 2 mol% sulfonamides at −24 °C and then, made recrystallization in order to increase the enantioselectivities. In 2006, bis-aryl thioureas were used as organocatalysts by Connon [11] et al. in that reaction. They synthesized 7 different 3-substituted indole derivatives with up to 50% ee, by using 10–20 mol% catalyst loading at −30 °C. After two years, almost under the same harsh reaction conditions (10% mol catalyst loading at −35 °C with benzene and DCE as solvent system) with Connon, the phosphoric acid was tested in model reaction by Akiyama [12] et al. They managed to synthesize 14 different products with high enantioselectivities up to 94% and moderate yields. In 2011, Zhang [13] and his co-workers used the 5 mol% phosphoric acids in the Friedel-Crafts alkylation. Unfortunately, they only managed to reach up to 47% ee with 23 different products at 20 °C. In 2016, Chen [14] et al. synthesized 12 different 3-substituted indole derivatives in the presence of 10 mol% secondary amine-amide organocatalyst with high enantioselectivities (up to 95% ee) and chemical yields at 35 °C (Scheme 1). In spite of these reports, a great demand has still been going on for improving the reaction conditions of that Friedel-Crafts alkylation of indole with nitroolefins.

Chiral bifunctional squaramides as an example to Brønsted base/H-bond donor organocatalysts are pioneered by Rawal [15] and since then, are being improved as well as tested in different type of reactions. In our research group, chiral bifunctional squaramides were synthesized [16–18] and evaluated named reactions such as Michael additions [17], Aza-Henry [19], Friedel-Crafts [20], Mannich reactions [21], and Sulfa-Michael addition [22]. Inspired by these studies, the Friedel-Crafts alkylation of indoles with nitroalkenes was tested in the presence of chiral bifunctional squaramides in order to improve the reaction conditions.

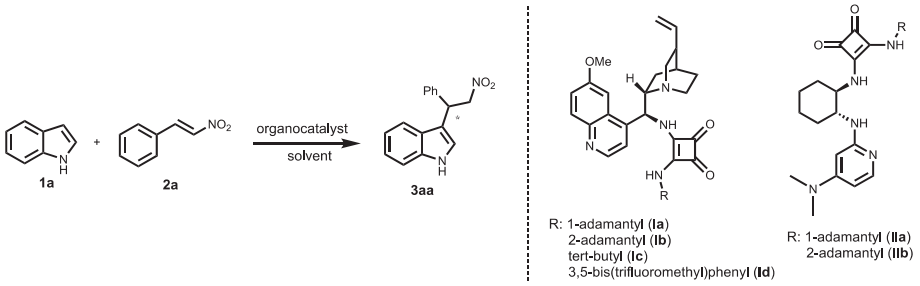
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Scheme 1. A literature comparison of **Ic** in organocatalysis **1a** + **2a.**

Table 1
Optimization Study.[a]



Entry	Cat.	Solvent	Cat. Load. (mol%)	Time (h)	Yield[b] (%)	ee[c] (%)
1	**Ia**	DCM	2	45	16	77
2	**Ib**	DCM	2	47	18	84
3	**Ic**	DCM	2	24	45	91
4	**Id**	DCM	2	24	14	8
5	**IIa**	DCM	2	44	56	rac
6	**IIb**	DCM	2	44	42	12
7	**Ia**	DCM	5	45	20	81
8	**Ib**	DCM	5	45	19	88
9	**Ic**	DCM	5	24	38	89
10	**Ic**	DCM	10	24	54	91
11	**Ic**	Chloroform	2	51	44	72
12	**Ic**	Xylene	2	44	24	78
13	**Ic**	Dioxane	2	92	trace	56
14	**Ic**	Toluene	2	51	26	82
15[d]	**Ic**	Toluene	2	46	34	78
16[e]	**Ic**	DCM	2	2	32	71
17[f]	**Ic**	DCM	2	46	26	84
18[g]	**Ic**	DCM	2	48	23	88

[a] Reaction conditions: **1a** (0.2 mmol, 1 eq.), **2a** (0.2 mmol, 1 eq.), catalyst, DCM (0.5 mL).
[b] Isolated yields.
[c] Determined by HPLC with chiral stationary phase.
[d] Temperature is 50 °C.
[e] H^+ sponge is used as an additive.
[f] NaOAc is used as an additive.
[g] Concentration is 1 M.

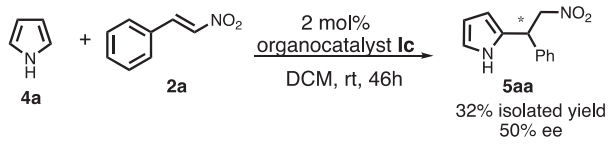
Results and discussion

Chiral bifunctional quinine (**Ia**, **Ib**, **Ic** and **Id**) and 2-AminoDMAP (**IIa** and **IIb**) based squaramide organocatalysts were evaluated in our model Friedel-Crafts alkylation of indole **(1a)** with *trans*-β-nitrostyrene **(2a)**.

Firstly, all six organocatalysts were tested in that reaction by using 2 mol% catalyst loading in DCM at room temperature. While organocatalysts (**Ia**, **Ib**, and **Ic**) afforded the product **3aa** with high enantioselectivity values (Table 1, entries 1–3, respectively), organocatalysts (**Id**, **IIa** and **IIb**) gave nearly racemic product **3aa** (Table 1, entries 4–6, respectively).

Further optimization studies continued with quinine based squaramide organocatalysts. Due to low chemical yield values with 2 mol%, we increased the catalyst loading to 5 mol% and 10 mol% (Entries 7–10, respectively). By comparing the results with 2 mol %, no improvement was observed in terms of chemical yield and reaction duration parameters whereas a slight increase in ee values for organocatalyst **Ia** and **Ib** as 77% to 81% and 84% to 88% (Entries 7–8, respectively). In the light of these data, organocatalyst **Ic** was chosen as the best one for Friedel-Crafts alkylation of indole **(1a)** with *trans*-β-nitrostyrene **(2a)** in terms of enantioselectivity and chemical yield. In the further optimization studies, although the effect of solvent (Entries 11–14), temperature (Entry 15), additive (Entry 16–17) and concentration (Entry 18) were investigated, we could not get better result than entry 3.

With the optimized condition in hand, the scope of the stereoselective organocatalytic Friedel-Crafts alkylation reaction was explored using 14 nitroolefin and 4 indole derivatives to observe the effect of electron-donating and electron-withdrawing groups. The results were summarized in Table 2.



Scheme 2. Friedel-Crafts Alkylation of Pyrrole **(4a)** with *trans*-β-nitrostyrene **(2a)**.

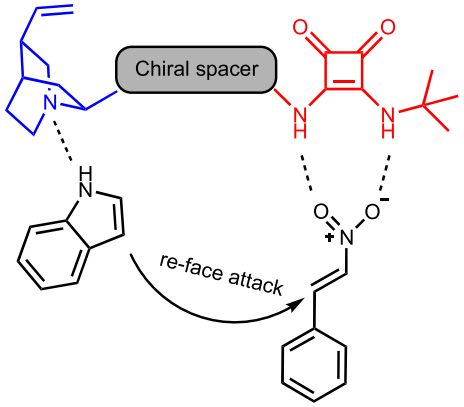
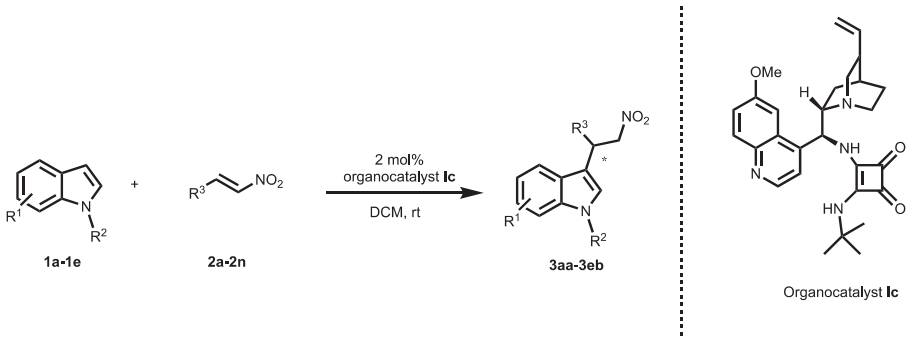


Fig. 1. A proposed transition state model.

Most of nitroolefins bearing either electron-donating or withdrawing groups afforded the Friedel-Crafts alkylation product [23] with excellent enantioselectivities (up to 92%) and moderate chemical yield values (up to 80%). However, the thienyl substituted product **3ag** resulted in lower enantioselectivity value compared to

Table 2
Derivatization Study.[a]



Entry	Indole	R^1	R^2	R^3	Product	Time (h)	Yield[b] (%)	ee[c] (%)
1	**1a**	H	H	Ph **(2a)**	**3aa**	24	45	91
2	**1a**	H	H	4-$MeOC_6H_4$ **(2b)**	**3ab**	44	27	85
3	**1a**	H	H	4-MeC_6H_4 **(2c)**	**3ac**	46	38	91
4	**1a**	H	H	4-ClC_6H_4 **(2d)**	**3ad**	49	32	87
5	**1a**	H	H	4-BrC_6H_4 **(2e)**	**3ae**	51	22	89
6	**1a**	H	H	2-Furyl **(2f)**	**3af**	28	74	87
7	**1a**	H	H	2-Thienyl **(2g)**	**3ag**	30	78	56
8	**1a**	H	H	2-ClC_6H_4 **(2h)**	**3ah**	47	80	90
9	**1a**	H	H	2-$MeOC_6H_4$ **(2i)**	**3ai**	50	78	80
10	**1a**	H	H	3-BrC_6H_4 **(2j)**	**3aj**	42	57	74
11	**1a**	H	H	3-$MeOC_6H_4$ **(2k)**	**3ak**	47	37	92
12	**1a**	H	H	2,4-$(Cl)_2C_6H_3$ **(2l)**	**3al**	24	33	77
13	**1a**	H	H	2,5-$(MeO)_2C_6H_3$ **(2m)**	**3am**	54	49	76
14	**1a**	H	H	2-$PhCH_2OC_6H_4$ **(2n)**	**3an**	54	79	69
15	**1b**	5-OBn	H	Ph **(2a)**	**3ba**	46	63	73
16	**1c**	7-OBn	H	Ph **(2a)**	**3ca**	46	55	67
17	**1d**	7-Br	H	Ph **(2a)**	**3da**	47	43	>99
18	**1e**	H	Me	4-$MeOC_6H_4$ **(2b)**	**3eb**	24	15	18

[a] Reaction conditions: **1a-1e** (0.2 mmol, 1 eq.), **2a-2n** (0.2 mmol, 1 eq.), catalyst, DCM (0.5 mL).
[b] Entries 1–11, Conversions, determined by GC–MS & entries 12–18, Isolated yields.
[c] Determined by HPLC with chiral stationary phase.

other derivatives (Table 2, entry 7). The stereoselectivity of Friedel-Crafts reactions were apparently insensitive to the substitution pattern on aromatic ring (*o*-, *m*-, or *p*-) of nitroolefins, as well as the electronic nature (entries 1–14 of Table 2).

Also, indole derivatives [24] and pyrrole were tested (Table 2, entries 15–18 & Scheme 2).

The absolute configuration of products **3aa**-**3eb** and **5aa** were assigned as **S** by comparing HPLC data and optical rotation values with literature.[7d,6h,6k,8c,7c] We proposed a transition state model in Fig. 1 to understand the selectivity of Friedel-Crafts alkylation of indole **(1a)** with *trans*-β-nitrostyrene **(2a)** in the presence of bifunctional quinine derived squaramide organocatalyst **Ic**. In this model, the deprotonation of indole **(1a)** occurs by a H-bond interaction with the basic part of the catalyst while acidic part activates the *trans*-β-nitrostyrene **(2a)** through double H-bond. Then, coordinated indole **(1a)** to basic site of organocatalyst **Ic** attacks the re-face of the activated *trans*-β-nitrostyrene **(2a)** and give the expected product. This transition state model is supported with entry 2 and 18 of Table 2.

Conclusion

To sum up, the Friedel-Crafts alkylation of indoles with nitroolefins was tested in the presence of sterically encumbered *tert*-butyl squaramide/quinine in this study. By usage of different nitroolefin and indole derivatives, 3-substituted indole products were synthesized with excellent enantioselectivities (up to >99% ee) and moderate chemical yields (up to 80%) by carrying out the reaction at room temperature and only using 2 mol% catalyst loading.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153153.

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