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# HETEROGENEOUSLY ORGANOCATALYTIC, ENANTIOSELECTIVE FRIEDEL-CRAFTS ALKYLATION OF INDOLE WITH 3,3,3-TRIFLUOROPYRUVATE

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**Abstract** – The bifunctional tertiary amine-squaramide catalyst was synthesized with diphenylethylenediamine as the chiral framework and successfully catalyzed the asymmetric Friedel-Crafts alkylation reaction between indole and trifluoropyruvate. A series of trifluoromethylated indole derivatives were obtained with high yield (up to 95%) and moderate to good enantioselectivity (up to 76% ee). The reaction proceeds in heterogeneous system, and the catalyst can be recovered by simple filtration and recycled.

Fluorine atom, as the biological isostere of hydrogen atom, has a series of special properties, including pseudo-mimicking effect, blocking effect, spatial effect and inductive effect, etc. Therefore, fluorinated compounds are usually used in pharmaceuticals, agrochemicals, functional materials and other related fields.[1] Moreover, indoles are the core structure of many natural products and potential drugs, and the preparation of chiral indole derivatives continues to be a fascinating subject in organic synthesis. The enantioselective Friedel-Crafts alkylation reaction is one of the most convenient and direct methods approaches to obtain chiral indole derivatives. In particular, the Friedel–Crafts alkylation of indoles with trifluoropyruvate provides a useful pathway to provide tertiary alcohols bearing a neighboring trifluoromethyl group and ester derivatives thereof.

In the past several decades, the Friedel-Crafts alkylation reaction of indoles with trifluoropyruvate has attracted much attention.[2] The numerous methodologies have been found to be effective in catalyzing the enantioselective Friedel-Crafts alkylation reactions: (1) transition-metal, alkaline-earth metal and rare-earth metal complexes catalysis,[3,4] such as chiral copper,[3a-d] titanium,[3e] zinc,[3f,g] iridium,[3h] calcium,[3i]

ytterbium,[3j] and scandium[3k] complexes, especially $C_2$-symmetric ligands copper complex proved to be an extremely effective catalyst; (2) organocatalysis, such as cinchona alkaloids,[4a] phosphoric acid,[4b,c] and $C_3$-symmetric cinchonine-squaramides,[4d] etc.[4e] Despite the many available processes, most existing methods rely on the application of chiral metal catalysts, so the development of new, economic and easily recycled organocatalyzed methods for the synthesis of trifluoromethylated compounds is still in great demand.

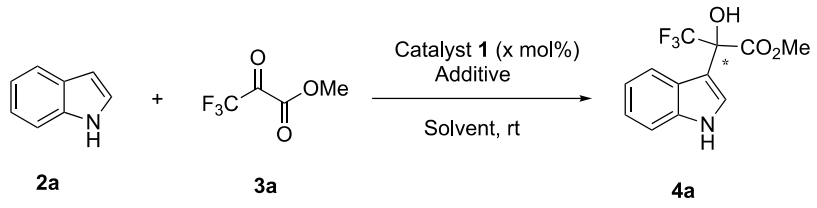
The chiral $C_3$-symmetric cinchonine-squaramides have been demonstrated to be effective by Dong and co-workers.[4d] Nevertheless, the Friedel-Crafts alkylation reaction of 4-hydroxyindole with ethyl trifluoropyruvate catalyzed by the single cinchona-derived squaramide only provided reaction product in a racemic form.[5] To the best of our knowledge, the amine catalysts that catalyze the asymmetric Friedel-Crafts alkylation reaction mainly include MacMillan catalysts, cinchona alkaloids, and proline derivatives,[6] tertiary amine-thiourea/squaramide bifunctional catalysts have not yet been systematically researched. Therefore, we attempted the Friedel-Crafts alkylation reaction of indoles with trifluoropyruvate using tertiary amine-thiourea/squaramide bifunctional catalysts.

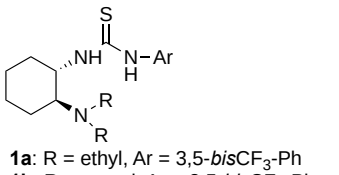
On the basis of above concept, we synthesized catalysts **1a-h** according to the literature.[7] Our investigation began with the evaluation of the ability of chiral tertiary amine-thiourea/squaramide bifunctional catalysts **1a-h** to promote the Friedel-Crafts reaction of unprotected indole **2a** with methyl trifluoropyruvate **3a** using *n*-butyl ether as the solvent. We were able to obtain the desired 3-alkylated indole **4a** using 10 mol% tertiary amine-thiourea catalyst with (1*R*, 2*R*)-cyclohexanediamine skeleton (Table 1, entries 1-5) with poor enantioselectivity although in good yield, and only tertiary amine-squaramide catalyst obtained a moderate ee value (entry 6). When using tertiary amine catalysts with (1*R*, 2*R*)-diphenylethylenediamine skeleton, the target product has been achieved with moderate to high yields and good ee (entries 7-8). Among them, the catalyst **1h** gave the best yield and ee value (entry 8).

In further investigations, variations of the reaction conditions, including catalyst loading, solvent, solvent loading, temperature, additive on the yield and enantioselectivity of the Friedel-Crafts reaction between methyl trifluoropyruvate and indole. When catalyst loading was increased to 20 mol%, the enantioselectivity increased from 58% to 69% (entry 10). Catalyst loading decrease was detrimental for both yield and enantiocontrol (entry 11). Several solvents were tested in the presence of 20 mol% catalyst at room temperature. Although the catalyst **1h** can not dissolve in these solvents, the reaction proceeded smoothly in non-protic solvent (*n*-hexane, toluene, $CH_2Cl_2$, $Cl_2CHCHCl_2$, and THF) with different enantioselectivities (17-67% ee, entries 12-16, respectively), and no product was observed in MeOH (entry 17), which may be caused by the hydrogen of the hydroxyl group is easier to lose than the hydrogen on the N atom of indole. The catalyst **1h** dissolves well in DMF, DMSO and 1,4-dioxane, but the reaction proceeded only in 1,4-dioxane (entries 18-20). The results indicated that *n*-butyl ether was

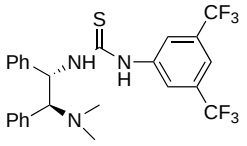
effective for the reaction. Due to the enantioselectivity was strongly dependent on the concentration,[4c,8] in order to suppress the background reaction, we carried out the reaction in dilute solution (0.05 mol/L) and found that running the reaction under dilute conditions improved the ee to 73% (entry 21). Unfortunately, adding additives or lowering the reaction temperature can not increase the enantioselectivity of the reaction.[9]

**Table 1.** Optimization of catalysts and reaction conditions[a]

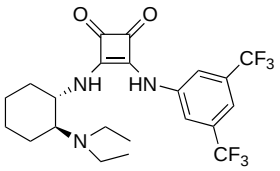


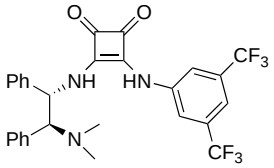
**1a**: R = ethyl, Ar = 3,5-*bis*$CF_3$-Ph
**1b**: R = propyl, Ar = 3,5-*bis*$CF_3$-Ph
**1c**: R = -$(CH_2)_4$-, Ar = 3,5-*bis*$CF_3$-Ph
**1d**: R = -$(CH_2)_5$-, Ar = 3,5-*bis*$CF_3$-Ph
**1e**: R = ethyl, Ar = 4-$NO_2$-Ph



**1g**



**1f**



**1h**

| Entry | Catalyst | Solvent | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|
| 1 | **1a** | *n*-$Bu_2O$ | 95 | 2 |
| 2 | **1b** | *n*-$Bu_2O$ | 89 | 6 |
| 3 | **1c** | *n*-$Bu_2O$ | 90 | 23 |
| 4 | **1d** | *n*-$Bu_2O$ | 88 | 10 |
| 5 | **1e** | *n*-$Bu_2O$ | 81 | 5 |
| 6 | **1f** | *n*-$Bu_2O$ | 72 | 53 |
| 7 | **1g** | *n*-$Bu_2O$ | 91 | 47 |
| 8 | **1h** | *n*-$Bu_2O$ | 92 | 58 |
| 9 | **1h** (15 mol%) | *n*-$Bu_2O$ | 93 | 66 |
| 10 | **1h** (20 mol%) | *n*-$Bu_2O$ | 96 | 69 |
| 11 | **1h** (5 mol%) | *n*-$Bu_2O$ | 85 | 57 |
| 12 | **1h** | *n*-hexane | 65 | 67 |
| 13 | **1h** | toluene | 92 | 23 |
| 14 | **1h** | $CH_2Cl_2$ | 89 | 17 |
| 15 | **1h** | $Cl_2CHCHCl_2$ | 90 | 53 |
| 16 | **1h** | THF | 82 | 58 |
| 17 | **1h** | MeOH | - | - |
| 18 | **1h** | DMF | - | - |
| 19 | **1h** | DMSO | - | - |

| | | | | |
|---|---|---|---|---|
| 20 | **1h** | 1,4-dioxane | 38 | 20 |
| 21[d] | **1h** | *n*-$Bu_2O$ | 95 | 73 |

[a]Reaction conditions: 0.1 mmol **2a**, 0.12 mmol methyl trifluoropyruvate **3a**, 1.0 mL *n*-$Bu_2O$.

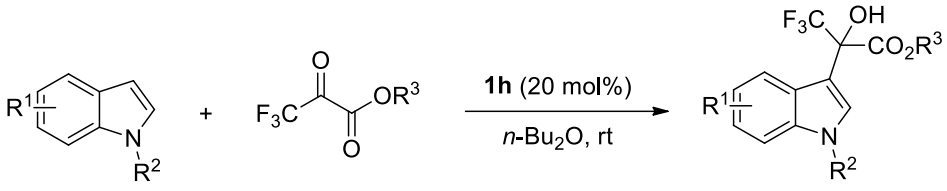
[b]Isolated yield.

[c]Determined by HPLC analysis on a chiral stationary phase.

[d]2.0 mL *n*-$Bu_2O$ was added.

With the optimized conditions in hand, we tested a variety of substituted indoles under the optimal reaction conditions. As summarized in Table 2, the substituted group of indoles played an important role in controlling the reaction activity and enantioselectivity. Most indoles bearing different groups furnished corresponding products in good yield and good enantioselectivity. Substrates with the electron-donating group Me and MeO at 5-position of indole gave good results in terms of an 76% ee (entries 2-3). Of note, active group OH was also tolerated (entry 4). Halogen groups (F or Br) on indoles were detrimental to this catalytic asymmetric Friedel-Crafts reaction, and most of the desired products were obtained in slightly reduced enantioselectivities (entries 5-6). Unfortunately, electron-withdrawing or electron-donating substituent on the 7-position of indole, the reaction activity and enantioselectivity were decreased (entries 7-9). 2-Methyl substituted indoles were also tested, and the resulting ee values were poor (entry 10). The effect of steric hinderance might be responsible for the decrease in enantioselectivity. Furthermore, when N-methylindole was treated with methyl trifluoropyruvate under the optimal conditions, racemic compound was observed (entry 11). This finding demonstrated that the hydrogen atom on the N atom of indole was extremely important to enantioselectivity. Finally, ethyl trifluoropyruvate was similar to methyl trifluoropyruvate in reaction activity and enantioselectivity. Fortunately, after **4a** was crystallized with dichloromethane and *n*-hexane, the ee value of the crystal decreased, but the ee value of the mother liquor increased to 88%.

**Table 2.** Catalytic asymmetric Friedel-Crafts reaction of various indoles **2** and trifluoropyruvate




**2a~l** **3a~b** **4a~l**

| Entry | $R^1$ | $R^2$ | $R^3$ | Reaction time (h) | Yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | H | H | Me | 6 | 95 | 73 (88)[c] |
| 2 | 5-Me | H | Me | 12 | 93 | 76 |
| 3 | 5-OMe | H | Me | 12 | 92 | 76 |
| 4 | 5-OH | H | Me | 36 | 82 | 71 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | 5-Br | H | Me | 36 | 88 | 70 |
| 6 | 6-F | H | Me | 36 | 89 | 68 |
| 7 | 7-Et | H | Me | 16 | 92 | 66 |
| 8 | 7-Cl | H | Me | 36 | 86 | 52 |
| 9 | 7-$NO_2$ | H | Me | 106 | 67 | 24 |
| 10 | 2-Me | H | Me | 106 | 72 | 16 |
| 11 | 1-Me | H | Me | 36 | 81 | <1 |
| 12 | H | H | Et | 6 | 94 | 72 |

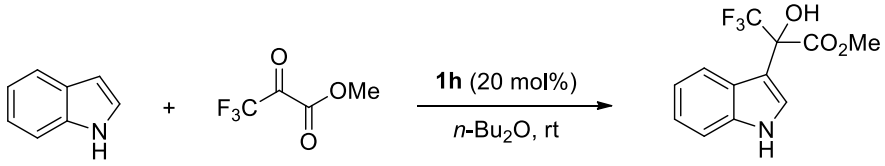
[a]Isolated yield.

[b]Determined by HPLC analysis on a chiral stationary phase.

[c]The value in parentheses indicates the ee after crystallization.

The poor solubility of the catalyst **1h** in *n*-butyl ether allows its recycling. To obtain the information on the recycling ability of the catalyst, **1h** was recovered in the Friedel-Crafts alkylation of **2a** and methyl trifluoropyruvate **3a**, which was expanded to 2 mmol (20 times). TLC monitoring the disappearance of indole, the reaction was simply filtered with a Buchner funnel. After the catalyst (filter cake) was rinsed with a small amount of cold *n*-butyl ether, which was put into the next reaction cycle. As shown in Table 3, our results indicated catalyst **1h** could be reused there times almost no loss of activity and selectivity. The state of substrates and catalysts during the reaction was shown in the supporting information as photograph.

**Table 3.** Recycling experiments of catalyst **1h** in the Friedel-Crafts alkylation of **2a** with methyl trifluoropyruvate **3a**




**2a** 2 mmol **3a** **4a**

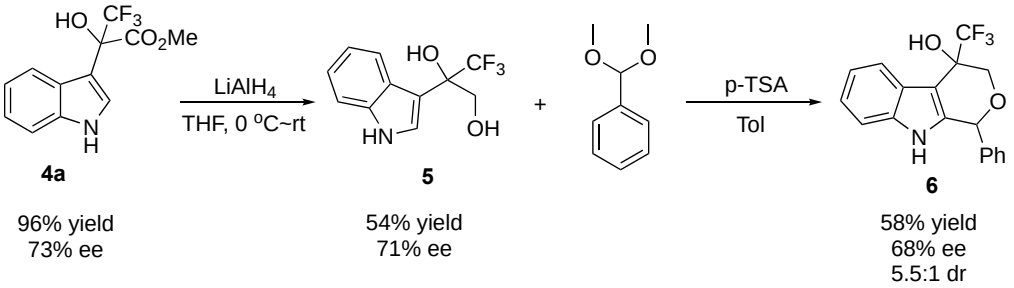
| Cycle No. | Yield (%)[a] | ee (%)[b] | Recovery rate (%) |
|---|---|---|---|
| 1 | 96 | 73 | 85 |
| 2 | 95 | 70 | 91 |
| 3 | 94 | 69 | 93 |

[a]Isolated yield.

[b]Determined by HPLC analysis on a chiral stationary phase.

The 1,3,4,9-tetrahydropyrano[3,4-*b*]indole scaffold is of considerable importance in medicinal chemistry. Compounds with this core scaffold exhibit attractive extensive medicinal and biological activities.[10]

Optically active **4a** was reduced by $LiAlH_4$ to obtain chiral diol **5**. The Pictet-Splengler reaction between diol **5** and acetal obtains compound **6** with 1,3,4,9-tetrahydropyrano[3,4-*b*]indole scaffold (Scheme 1). The ee value of the product dropped slightly during the whole reaction process.




**Scheme 1.** Synthesis of 1,3,4,9-tetrahydropyrano[3,4-*b*]indole derivative **6**

In summary, bifunctional tertiary amine-squaramide catalysts were demonstrated to be effective for the enantioselective Friedel-Crafts reaction of indoles with trifluoropyruvates. In addition, catalyst **1h** can also be reused there times almost no loss of activity and selectivity, and trifluoromethylated indole can be converted into 1,3,4,9-tetrahydropyrano[3,4-*b*]indole derivative by simple steps.

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## SUPPORTING INFORMATION

Supplementary (Optimization of the reaction conditions, HPLC chromatograms, $^{1}H$ and $^{13}C$ NMR chromatograms, etc.) data associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27465/104/2.

## REFERENCES AND NOTES

1. (a) Y. Zhu, J. L. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho, and F. D. Toste, *Chem. Rev*., 2018, **118**, 3887; (b) H. J. Lai, Q. Q. Zhao, Z. Y. Chen, H. Chen, P. J. Chao, Y. L. Zhu, Y. W. Lang, N. Zhen, D. Z. Mo, Y. Z. Zhang, and F. He, *Joule*, 2020, **4**, 688.
2. (a) X. Han, W. J. Ouyang, B. Liu, W. Wang, P. Tien, S. Wu, and H. B. Zhou, *Org. Biomol. Chem*., 2013, **11**, 8463; (b) D. R. Adams, A. Abraham, J. Asano, C. Breslin, C. A. J. Dick, U. Ixkes, B. F. Johnston, D. Johnston, J. Kewnay, S. P. Mackay, S. J. MacKenzie, M. McFarlane, L. Mitchell, D.

Spinks, and Y. Takano, *Bioorg. Med. Chem. Lett*., 2007, **17**, 6579; (c) T. Sumiyoshi, K. Tojo, D. Urabe, and M. Tobe, *Tetrahedron: Asymmetry*, 2011, **22**, 153.

3. (a) M. P. A. Lyle, N. D. Draper, and P. D. Wilson, *Org. Lett*., 2005, **7**, 901; (b) S. Nakamura, K. Hyodo, Y. Nakamura, N. Shibata, and T. Toru, *Adv. Synth. Catal*., 2008, **350**, 1443; (c) C. Wolf and P. Zhang, *Adv. Synth. Catal*., 2011, **353**, 760; (d) W. Zhuang, N. Gathergood, R. G. Hazell, and K. A. Jørgensen, *J. Org. Chem*., 2001, **66**, 1009; (e) H. M. Dong, H. H. Lu, L. Q. Lu, C. B. Chen, and W. J. Xiao, *Adv. Synth. Catal*., 2007, **349**, 1597; (f) Y. Z. Hua, J. W. Chen, H. Yang, and M. C. Wang, *J. Org. Chem*., 2018, **83**, 1160; (g) Y. H. Hui, W. L. Chen, W. T. Wang, J. Jiang, Y. F. Cai, L. L. Lin, X. H. Liu, and X. M. Feng, *Adv. Synth. Catal*., 2010, **352**, 3174; (h) D. Carmona, M. P. Lamata, A. Sánchez, F. Viguri, R. Rodríguez, L. A. Oro, C. H. Liu, S. Díez-Gonzálezb, and F. Maseras, *Dalton Trans*., 2014, **43**, 11260; (i) M. Rueping, T. Bootwicha, S. Kambutong, and E. Sugiono, *Chem. Asian J*., 2012, **7**, 1195; (j) G. Grach, A. Dinut, S. Marque, J. Marrot, R. Gil, and D. Prim, *Org. Biomol. Chem*., 2011, **9**, 497; (k) A. Aillerie, V. Rodriguez-Ruiz, R. Carlino, F. Bourdreux, R. Guillot, S. Bezzenine-Lafollée, R. Gil, D. Prim, and J. Hannedouche, *ChemCatChem*, 2016, **8**, 2455.
4. (a) B. Török, M. Abid, G. London, J. Esquibel, M. Török, S. C. Mhadgut, P. Yan, and G. K. S. Prakash, *Angew. Chem. Int. Ed*., 2005, **44**, 3086; *Angew. Chem*., 2005, **117**, 3146; (b) J. Nie, G. W. Zhang, L. Wang, D. H. Zheng, Y. Zheng, and J. A. Ma, *Eur. J. Org. Chem*., 2009, 3145; (c) W. Kashikura, J. Itoh, K. Mori, and T. Akiyama, *Chem. Asian J*., 2010, **5**, 470; (d) X. Han, B. Liu, H. B. Zhou, and C. Dong, *Tetrahedron: Asymmetry*, 2012, **23**, 1332; (e) S. Marque, V. Razafimahaléo, A. Dinut, G. Grach, D. Prim, X. Moreaua, and R. Gil, *New J. Chem*., 2013, **37**, 2683.
5. M. Montesinos-Magraner, C. Vila, G. Blay, I. Fernández, M. C. Muñoz, and J. R. Pedro, *Org. Lett*., 2017, **19**, 1546.
6. For reviews, see: (a) V. Terrasson, R. M. Figueiredo, and J. M. Campagne, *Eur. J. Org. Chem*., 2010, 2635; (b) G. Bartoli, G. Bencivenni, and R. Dalpozzo, *Chem. Soc. Rev*., 2010, **39**, 4449; (c) M. Bandini, A. Melloni, and A. Umani-Ronchi, *Angew. Chem. Int. Ed*., 2004, **43**, 550; *Angew. Chem*., 2004, **23**, 560; (d) M Bandini and A. Eichholzer, *Angew. Chem. Int. Ed*., 2009, **48**, 9608; *Angew. Chem*., 2009, **121**, 9786.
7. (a) S.-Y. Hsieh and J. W. Bode, *Org. Lett*., 2016, **18**, 2098; (b) Y. Fukata, T. Okamura, K. Asano, and S. Matsubara, *Org. Lett*., 2014, **16**, 2184; (c) E. Massolo, M. Benaglia, A. Genoni, R. Annunziata, G. Celentano, and N. Gaggero, *Org. Biomol. Chem*., 2015, **13**, 5591; (d) N. R. Amarasinghe, P. Turner, and M. H. Todd, *Adv. Synth. Catal*., 2012, **354**, 2954; (e) L.-N. Jia, J. Huang, L. Peng, L.-L. Wang, J.-F. Bai, F. Tian, G.-Y. He, X.-Y. Xu, and L.-X. Wang, *Org. Biomol. Chem*., 2012, **10**, 236; (f) Z. Z. Jing, X. B. Bai, W. C. Chen, G. Zhang, B. Zhu, and Z. Y. Jiang, *Org. Lett*., 2016, **18**, 260; (g) T.-Y. Liu, J. Long, B.-J. Li, L. Jiang, R. Li, Y. Wu, L.-S. Ding, and Y.-C.

Chen, *Org. Biomol. Chem*., 2006, **4**, 2097.

8. Y.-F. Sheng, Q. Gu, A.-J. Zhang, and S.-L. You, *J. Org. Chem*., 2009, **74**, 6899.
9. See Supporting Information.
10. (a) C. A. Demerson, L. G. Humber, N. A. Abraham, G. Schilling, R. R. Martel, and C. Pace-Asciak, *J. Med. Chem*., 1983, **26**, 1778; (b) M. G. LaPorte, T. L. Draper, L. E. Miller, C. W. Blackledge, L. K. Leister, E. Amparo, A. R. Hussey, D. C. Young, S. K. Chunduru, C. A. Benetatos, G. Rhodes, A. Gopalsamy, T. Herbertz, C. J. Burns, and S. M. Condon, *Bioorg. Med. Chem. Lett*., 2010, **20**, 2968; (c) S. Schunk, K. Linz, S. Frormann, C. Hinze, S. Oberbörsch, B. Sundermann, S. Zemolka, W. Englberger, T. Germann, T. Christoph, B.-Y. Kögel, W. Schröder, S. Harlfinger, D. Saunders, A. Kless, H. Schick, and H. Sonnenschein, *ACS Med. Chem. Lett*., 2014, **5**, 851.