Telescoped Interrupted Barton–Zard reaction/Friedel–Crafts Alkylation for the Synthesis of Pyrrolo[3,4-*b*]indole Cores

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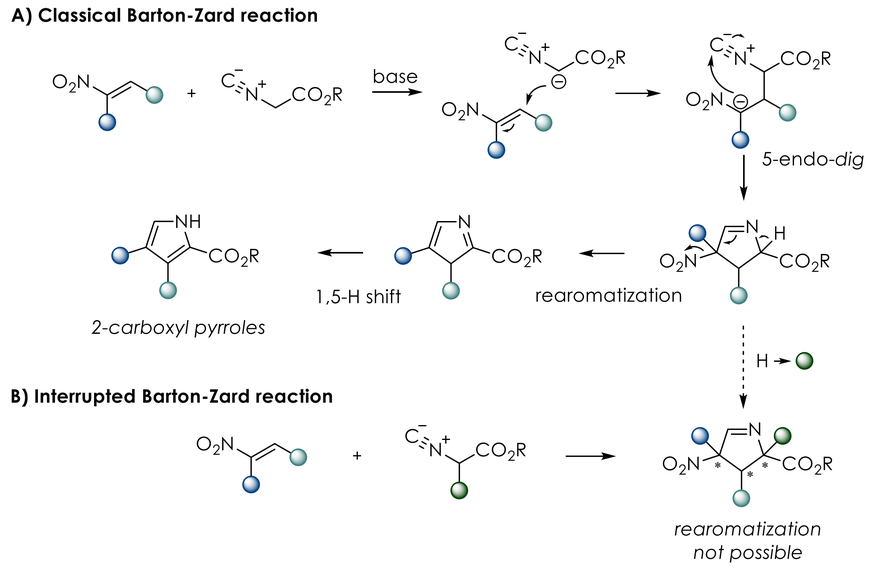
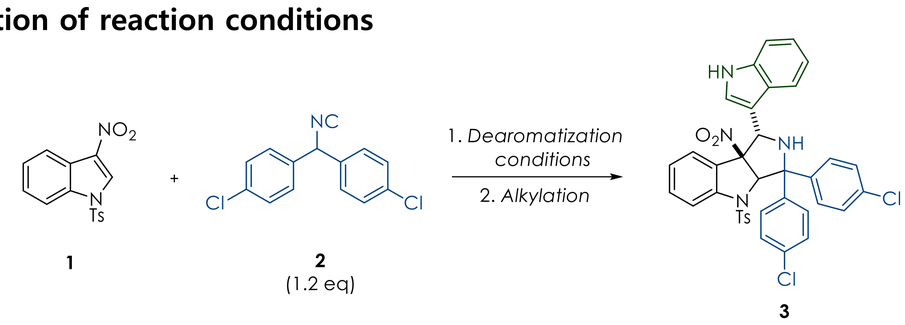
Introduction

The Barton–Zard reaction provides a direct route to 2-carboxyl-3,4-disubstituted pyrroles through the reaction of electron-deficient alkenes with α-isocyanoacetates under basic conditions. This transformation can also be extended to electron-deficient nitroarenes and nitroindoles, thereby enabling the synthesis of a diverse array of heteroaromatic structures. Due to the nature of its mechanism, the classical Barton–Zard reaction inherently generates aromatic pyrrole products (**A**). In contrast, the interrupted Barton–Zard reaction employs α-substituted isocyanoacetates as nucleophiles. These substitutions block the rearomatization step, thereby enabling the formation of non-aromatic heterocycles (**B**).



Herein, we report an interrupted Barton–Zard reaction between 3-nitroindoles and benzophenone-derived isocyanides, followed by *in situ* alkylation with aryl nucleophiles, enabling the synthesis of polycyclic structures bearing multiple aryl substituents.

Optimization of reaction conditions

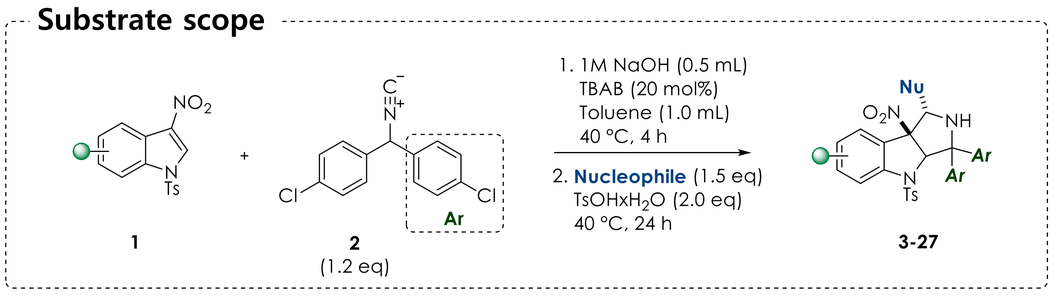


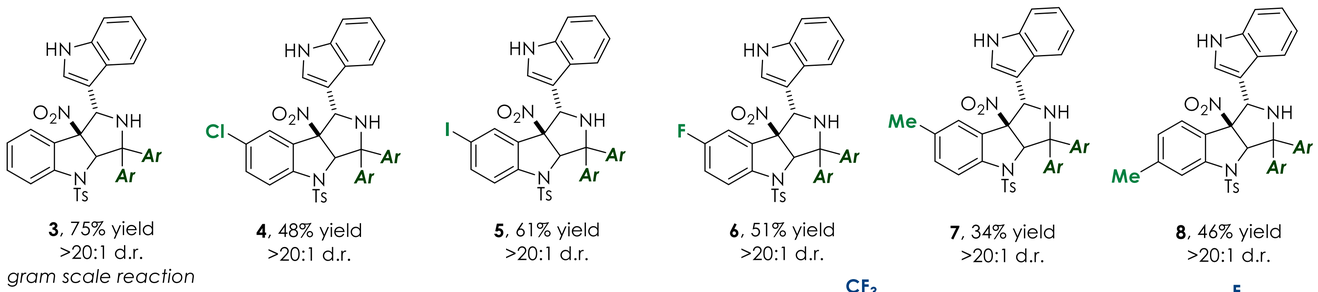
Entry	Base (3.0 eq)	Solvent	Temp. (°C)	Time (h)	*Then*	Yield (%)
1	Cs_2CO_3	Dichloroethane	rt	36	*Alkylation*	54
2	Cs_2CO_3	Dichloroethane	40	6	*Alkylation*	56
3[a]	Cs_2CO_3	Dichloroethane	40	48	*No dearomatization*	
4	-	Dichloroethane	40	48	*No dearomatization*	
5	Cs_2CO_3[b]	Dichloroethane	40	6	*Alkylation*	58
6[c]	Cs_2CO_3	Dichloroethane	40	6	*Alkylation*	56
7	Cs_2CO_3	Dichloromethane	40	6	*Alkylation*	51
8	Cs_2CO_3	Toluene	40	8	*Alkylation*	65
9	Cs_2CO_3	Chloroform	40	6	*Alkylation*	51
10	Cs_2CO_3	Toluene-water 1:1	40	48	*Alkylation*	55
11	K_2CO_3	Toluene	40	16	*Alkylation*	61
12	$NaOH_{(s)}$	Toluene	40	4	*Alkylation*	68
13	$KOH_{(s)}$	Toluene	40	4	*Alkylation*	58
14[d]	1M NaOH	Toluene	40	4	*Alkylation*	75
15[d]	1M NaOH	Toluene	rt	8	*Alkylation*	73
16[e]	1M NaOH	Toluene	40	4	*Alkylation*	75

Alkylation (optimized conditions): $TsOHxH_2O$ (2.0 eq), Indole (1.5 eq), 40 °C, 24 h.

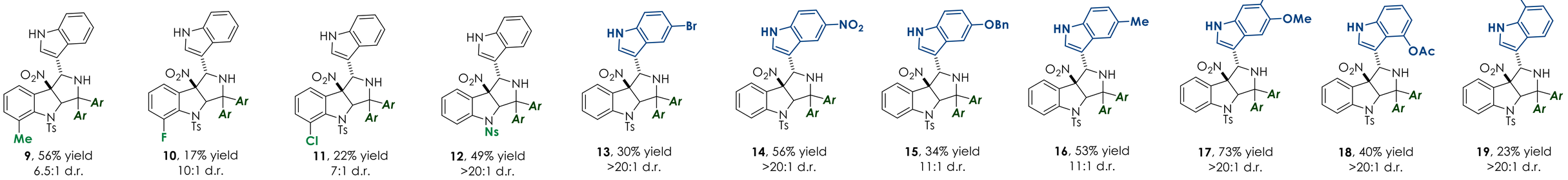
[a] No TBAB. [b] Cs_2CO_3 (5.0 eq). [c] **2** (1.5 eq). [d] 1M NaOH (0.5 mL). [e] 1M NaOH (1.0 mL).

Substrate scope

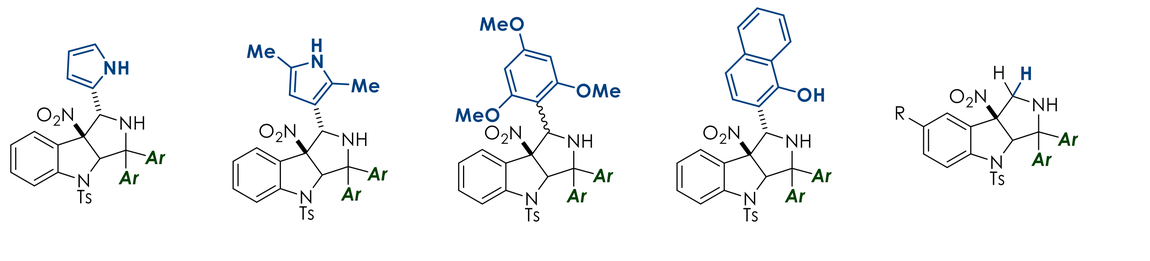




3, 75% yield, >20:1 d.r. *gram scale reaction*; **4**, 48% yield, >20:1 d.r.; **5**, 61% yield, >20:1 d.r.; **6**, 51% yield, >20:1 d.r.; **7**, 34% yield, >20:1 d.r.; **8**, 46% yield, >20:1 d.r.

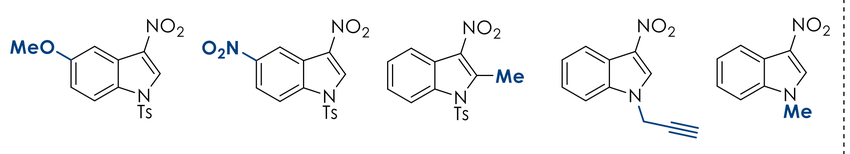


9, 56% yield, 6.5:1 d.r.; **10**, 17% yield, 10:1 d.r.; **11**, 22% yield, 7:1 d.r.; **12**, 49% yield, >20:1 d.r.; **13**, 30% yield, >20:1 d.r.; **14**, 56% yield, >20:1 d.r.; **15**, 34% yield, 11:1 d.r.; **16**, 53% yield, 11:1 d.r.; **17**, 73% yield, >20:1 d.r.; **18**, 40% yield, >20:1 d.r.; **19**, 23% yield, >20:1 d.r.



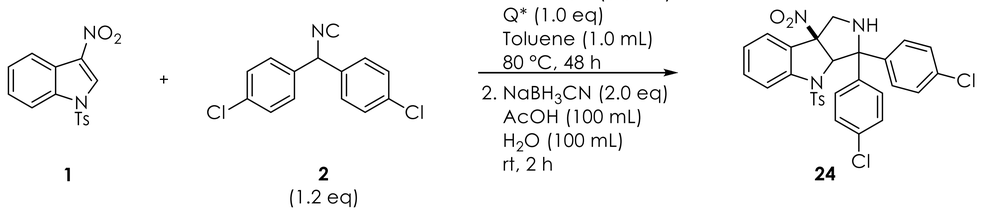
20, 55% yield, >20:1 d.r.; **21**, 44% yield, 10:1 d.r.; **22**, 32% yield, 1:1 d.r.; **23**, 18% yield, >20:1 d.r.; **24**, 70% yield, >20:1 d.r. (R=H)[a]; **25**, 68% yield, >20:1 d.r. (R=Cl)[a]; **26**, 59% yield, 1:1 d.r. (X=Cl); **27**, 18% yield, 1:1 d.r. (X=Br)

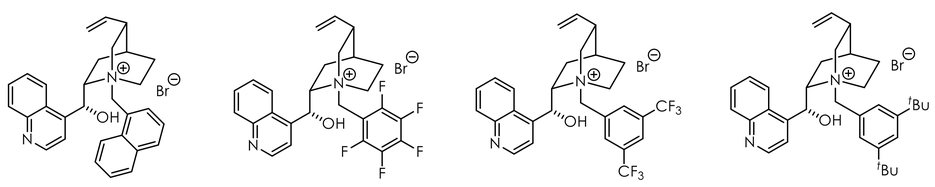
Dearomatization not observed with:



[a] *Reduction*: $NaBH_3CN$ (2.0 eq), AcOH (100 µL), H_2O (100 µL), Toluene, rt, 2 h.

Stereoselective reaction

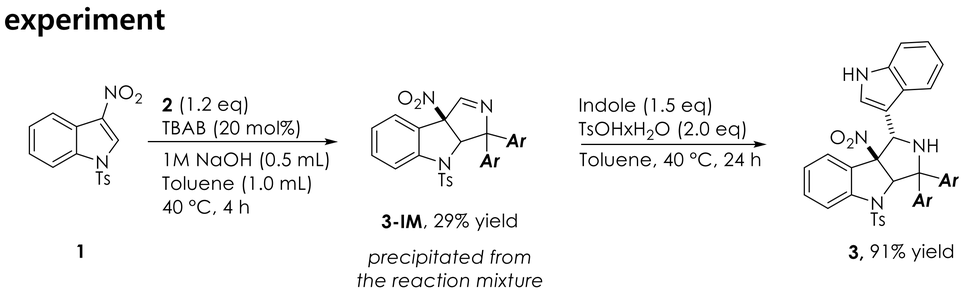




Q1 30% yield, 51:49 e.r., >20:1 d.r.; **Q2** 34% yield, 52:48 e.r., >20:1 d.r.; **Q3** 14% yield, 49:51 e.r., >20:1 d.r.; **Q4** 17% yield, 50:50 e.r., >20:1 d.r.

- Dearomatization step stopped after 48 hours – low conversion
- No conversion observed with the catalytic amounts of Q*

Control experiment



Conclusions

- Developed telescoped reaction for the synthesis of polycyclic structures bearing multiple aryl substituents
- Products obtained in moderate yields and mostly as single diastereomers
- Very limited substrate scope with respect to isocyanide derivatives (12 examined)
- Reactions with chiral catalysts have low conversion and yield products as racemates

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