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

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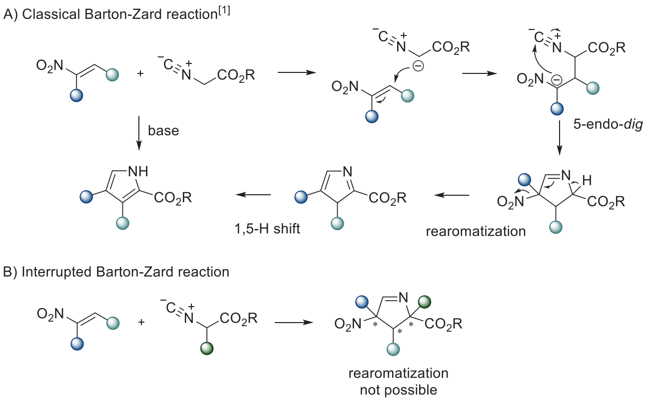
A dearomatization reaction between electron-deficient indoles and α,α-diaryl-substituted methyleneisocyanides, followed by *in situ* Friedel–Crafts alkylation, is described. In a telescoped reaction mediated by a Brønsted base in the first step and a Brønsted acid in the second step, aryl-substituted pyrrolo[3,4-b]indole cores are generally obtained in moderate-to-good yields and with high diastereoselectivity. The reaction tolerates a wide range of 3-nitroindoles and aryl nucleophiles; however, the substrate scope of isocyanide derivatives is limited. The developed methodology offers a modular approach for the synthesis of multi-substituted polycyclic cores.

1. Introduction

The Barton–Zard reaction, developed by Barton and Zard in 1985,[1] provides a direct route to 2-carboxyl-3,4-disubstituted pyrroles from electron-deficient alkenes and α-isocyanoacetates under basic conditions.[2–6] The reaction can also be performed with electron-deficient nitroarenes[7–9] and nitroindoles,[10–12] thereby generating a variety of heteroaromatic structures. Due to its reaction mechanism, the classical Barton–Zard reaction inherently cannot produce non-aromatic heterocyclic products (Scheme 1A).

In 2021, You and Yuan developed an interrupted Barton–Zard reaction by employing α-substituted isocyanoacetates as nucleophiles, which prevented the rearomatization step and enabled the formation of nonaromatic heterocyclic products (Scheme 1B). In a reaction catalyzed by an Ag(I)–amino-phosphine ligand system, 3-nitroindoles and α-substituted isocyanoacetates afforded chiral pyrrolo[3,4-b]indoles in high yields and with excellent enantioselectivities (Scheme 2A).[13]

A similar transformation was developed by Yuan and Zhao, in which the substrate scope also included 2-nitroindoles as electron-deficient arenes (Scheme 2B).[14] Blay and Pedro later developed an asymmetric organocatalytic interrupted Barton–Zard reaction using 2-nitrobenzofurans, mediated by a cupreine-ether-derived catalyst (Scheme 2C).[15]



Scheme 1. Classical vs interrupted Barton–Zard reaction.

Although these elegant examples provide straightforward access to pyrrolo[3,4-b]indole cores, the authors also report that the resulting products often lack stability. Consequently, specific handling procedures are recommended, or the products are immediately subjected to further transformations. We hypothesized that the interrupted Barton–Zard reaction could also be performed with α,α-diaryl-substituted methyleneisocyanides, enabling *in situ* transformation into highly functionalized hexahydropyrrolo[3,4-b]indole cores. In addition to the literature cited above, the past decade has seen growing interest in these cores, making them prominent targets in synthetic methodology development.[16–22] To the best of our knowledge, only one example exists of the synthesis of a 3,3-diaryl-substituted hexahydropyrrolo[3,4-b]indole polycyclic skeleton, reported as a postmodification reaction.[23]

Herein, we report an interrupted Barton–Zard reaction/Friedel–Crafts alkylation telescoped reaction for the synthesis of hexahydropyrrolo[3,4-b]indole cores bearing multiple aryl substituents. Under phase-transfer conditions and mediated by a Brønsted base, an interrupted Barton–Zard

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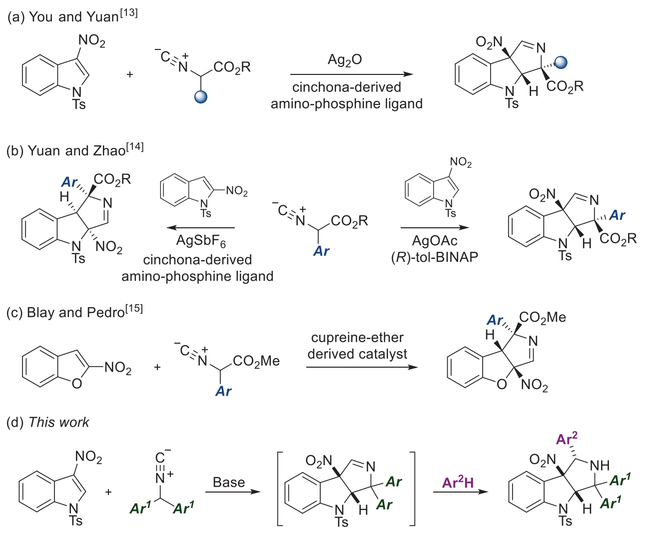


Scheme 2. Examples of the interrupted Barton–Zard reaction.

reaction between 3-nitroindoles and benzophenone-derived isocyanides affords pyrrolo[3,4-b]indole intermediates, which are subsequently alkylated *in situ* with heteroaromatic and aromatic nucleophiles under acidic conditions.

2. Results and Discussion

We began our investigation by screening reaction conditions for the dearomatization step (Table 1). Upon completion of the dearomatization reaction, as monitored by TLC, the resulting intermediate was subjected *in situ* to alkylation conditions (for the optimization of the Friedel–Crafts alkylation conditions, see Table S1 in the Supporting Information).

Initially, 3-nitroindole **1a** and isocyanide **2a** were combined with cesium carbonate as the base and tetrabutylammonium bromide (TBAB) as a phase-transfer catalyst in dichloroethane at room temperature. The dearomatization was completed after 36 h, and subsequent alkylation with indole afforded product **3** in 54% yield (Table 1, entry 1). Increasing the reaction temperature accelerated the dearomatization step, although the product yield remained essentially unchanged (entry 2). Control experiments in which either the base or TBAB catalyst was omitted resulted in the recovery of only the starting materials (entries 3 and 4). Increasing the amount of base or the isocyanide derivative **2a** had no significant effect on the reaction outcome (entries 5 and 6). Solvent screening revealed that conducting the transformation in toluene improved the product yield, albeit at the cost of a slower reaction rate (entry 8). Employing stronger Brønsted bases significantly shortened the de-aromatization step to 4 h, with the best yield (75%) obtained using 1 M NaOH (entry 14). Performing the reaction at room temperature under these conditions, or increasing the base amount, did not improve the yield but prolonged the dearomatization step in both cases (entries 15 and 16).

Therefore, the optimized conditions for the telescoped interrupted Barton–Zard reaction/Friedel–Crafts alkylation involve *N*-tosyl 3-nitroindole (1.0 equiv), an α,α-diaryl-substituted methyleneisocyanide derivative (1.2 equiv), and TBAB (20 mol%) in a toluene/1 M NaOH mixture (2:1) at 40 °C for 4 h, followed by addition of the aromatic nucleophile (1.5 equiv) and $TsOH{\cdot}H_2O$ (2.0 equiv) at 40 °C for 24 h (Table 1, entry 14).

With the optimized reaction conditions in hand, we next investigated the substrate scope and potential reaction limitations. We began by examining reactions with a variety of electron-deficient nitroindoles (Table 2). Isocyanide derivative **2a** reacted with several *N*-tosyl 3-nitroindoles, yielding products in moderate to good overall yields. When halogen atoms were introduced at the C5 position of the indole derivative, the reaction remained effective, providing products **4–6** in good yields. The reaction also proceeded efficiently when the methyl group was positioned at different locations on the indole benzene ring (products **7** and **8**). However, both the yield and diastereomeric ratio decreased when indoles bearing substituents at the C7 position were used (products **9–11**).

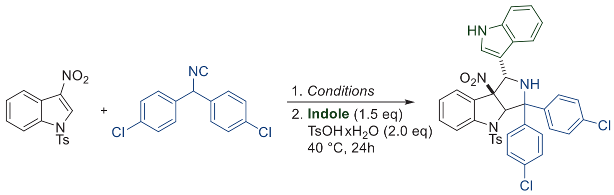
Interestingly, dearomatization did not occur when strong electron-donating or electron-withdrawing groups were introduced at the C5 position of the indole ring (**1e** and **1k**). The reaction was tolerant of replacing the *N*-tosyl protecting group with an *N*-nosyl (4-nitrophenylsulfonyl) group, successfully yielding product **12**. In contrast, *N*-alkyl 3-nitroindoles (**1o** and **1p**) did not undergo dearomatization, suggesting that the electrophilicity of 3-nitroindoles – necessary for this transformation — requires the presence of an additional electron-withdrawing *N*-protecting group. Furthermore, the interrupted Barton–Zard reaction failed to proceed with a substrate bearing a methyl group at the C2 position (**1m**), likely due to steric hindrance at the reaction center. The transformation was successfully performed on larger scales, albeit with slightly diminished yields for **3** (68% yield on a 1.58 mmol scale, 53% yield on a 2.85 mmol scale), and without any loss of diastereoselectivity.

Furthermore, we then turned our attention to exploring the substrate scope and limitations of the transformation with various nucleophiles (Table 3). In general, indoles bearing substituents at the C5 position afforded products in moderate to good yields, regardless of the electronic nature of the substituent, although indoles possessing benzyloxy or methyl groups exhibited somewhat lower diastereoselectivities (**13–16**). The reaction also tolerated Friedel–Crafts alkylation with 5-methoxy-6-trifluoromethylindole (**17**), as well as with indoles bearing substituents at the C4 and C7 positions (**18** and **19**, respectively).

Next, we explored the use of other heteroaromatic and aromatic nucleophiles in the transformation. Pyrrole and 2,5-dimethylpyrrole reacted smoothly under the optimized Friedel–Crafts alkylation conditions, affording products **20** (55% yield, >20:1 d.r.) and **21** (44% yield, 10:1 d.r.), respectively. Interestingly, the reaction with 1,3,5-trimethoxybenzene produced product **22** as a 1:1 mixture of diastereomers. When 1-naphthol was used as the nucleophile, the desired product **23** was obtained in low yield as a single diastereomer, while no alkylation product was observed with sesamol.

Although Friedel–Crafts alkylation was the primary focus of the second step in the telescoped reaction, we also explored

Table 1. Optimization of reaction conditions: de-aromatization.[a)]



1a 2a 3

Entry	Base	Solvent	Temp. (°C)	Time (h)	Then	3 (%)
1	Cs_2CO_3	DCE	rt	36	Alkylation	54
2	Cs_2CO_3	DCE	40	6	Alkylation	56
3[b)]	Cs_2CO_3	DCE	40	48	No dearomatization	
4	–	DCE	40	48	No dearomatization	
5	Cs_2CO_3[c)]	DCE	40	6	Alkylation	58
6[d)]	Cs_2CO_3	DCE	40	6	Alkylation	56
7	Cs_2CO_3	DCM	40	6	Alkylation	51
8	Cs_2CO_3	Toluene	40	8	Alkylation	65
9	Cs_2CO_3	$CHCl_3$	40	6	Alkylation	51
10	Cs_2CO_3	Toluene:H_2O 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[e)]	1 M NaOH	Toluene	40	4	Alkylation	75
15[e)]	1 M NaOH	Toluene	rt	8	Alkylation	73
16[f)]	1 M NaOH	Toluene	40	4	Alkylation	75

[a)] Reaction performed on 20 mg scale of **1a**. **2a** (1.2 equiv), Base (3.0 equiv), TBAB (20 mol%), Solvent (1.0 mL). Conversion of **1a** into dearomatized product monitored by TLC. The organic layer was filtered or decanted before employing alkylation conditions. In all entries, product **3** was isolated in >20:1 d.r. Relative configuration determined by NOESY NMR (see Supporting Information for details). [b)] No TBAB. [c)] Cs_2CO_3 (5.0 equiv). [d)] **2a** (1.5 equiv). [e)] 1 M NaOH (0.5 mL). [f)] 1 M NaOH (1.0 mL).

alternative transformations. Reduction of the imine double bond proceeded smoothly, yielding products **24** and **25** in 70% and 68% yield, respectively. No alkylation was observed when thiophenol was used as the nucleophile.

Investigation of the substrate scope using various α,α-diaryl-substituted methyleneisocyanides revealed limitations in the reaction efficiency and outcome (Table 4).

In addition to isocyanide derivative **2a**, only two out of twelve investigated isocyanide derivatives underwent the de-aromatization step under the optimized reaction conditions (for the full list of benzophenone-derived isocyanides examined, see Supporting Information). The reaction was successful with derivatives bearing halogen atoms in the *para* position of one of the phenyl substituents, although the rate of dearomatization was reduced. The isocyanide derivative containing a bromine substituent required a slightly elevated temperature to complete the dearomatization step. In both cases, products **26** and **27** were obtained as a 1:1 mixture of diastereomers.

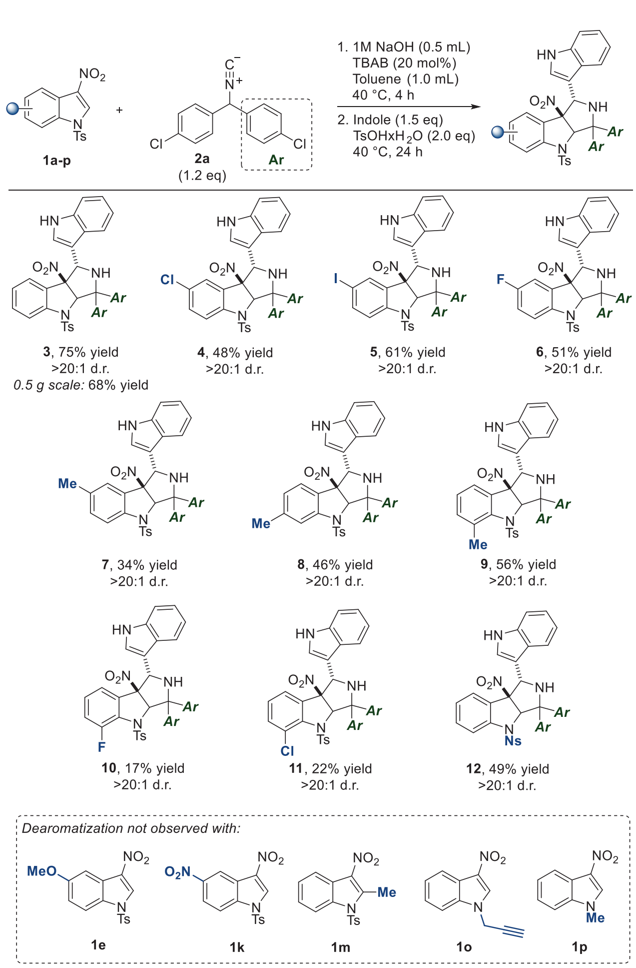
Two key conclusions can be drawn from the isocyanide substrate scope. First, the dearomatization step appears to be the limiting factor in the developed telescoped reaction. When an *ortho*-substituted diaryl methyleneisocyanide (compound **2f** in the Supporting Information) was employed, only the starting materials were recovered, even after extended reaction times and increased temperatures. This outcome is likely due to increased steric hindrance around the reaction center. In all other cases, although *N*-tosyl-3-nitroindole **1a** was fully consumed, only trace amounts of dearomatized products were detected by TLC, suggesting the occurrence of side reactions during the dearomatization process. Investigations into these side reactions are currently ongoing.

Second, the two phenyl groups in non-symmetrical benzophenone-derived isocyanides do not appear to differ sufficiently in steric or electronic properties to influence the diastereoselectivity of the resulting products.

To confirm that the reaction proceeds through the dearomatized imine intermediate **3-IM**, the intermediate was successfully isolated following the dearomatization step (Scheme 3).

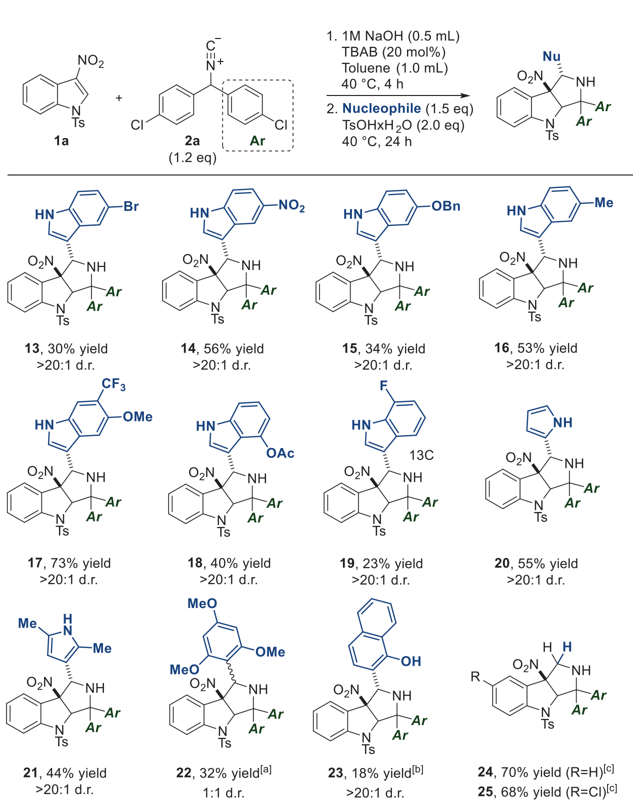
Under the optimized reaction conditions, intermediate **3-IM** was isolated from the reaction mixture by precipitation, affording a 29% yield. Furthermore, the subsequent reaction of **3-IM** with indole furnished product **3** in 91% isolated yield, supporting the involvement of **3-IM** as a key intermediate in the developed transformation.

Table 2. Substrate scope I: 3-nitroindoles.



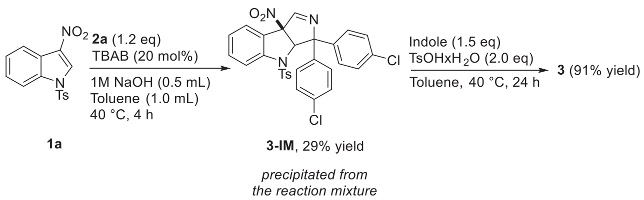
a) **1a** (0.5 g, 1.58 mmol), 68% yield, >20:1 d.r. b) **1a** (0.9 g, 2.85 mmol), 53% yield, >20:1 d.r.

Table 3. Substrate scope II: Nucleophiles.

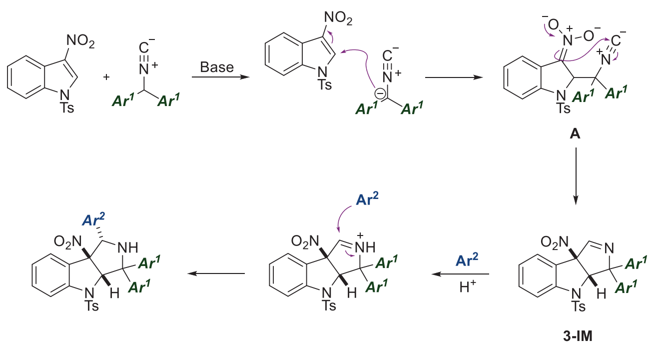


[a] Alkylation step: 72 hours. [b] Alkylation step: 48 hours. [c] Reduction conditions: $NaBH_3CN$ (2.0 eq), AcOH (100 µL), H_2O (100 µL), toluene, rt, 2 h. Product isolated in >20:1 d.r.

a) Alkylation step: 72 h. b) Alkylation step: 48 h. c) Reduction conditions: $NaBH_3CN$ (2.0 equiv), AcOH (100 µL), H_2O (100 µL), toluene, rt, 2 h. Products isolated in >20:1 d.r.



Scheme 3. Control experiment.



Scheme 4. Proposed reaction mechanism.

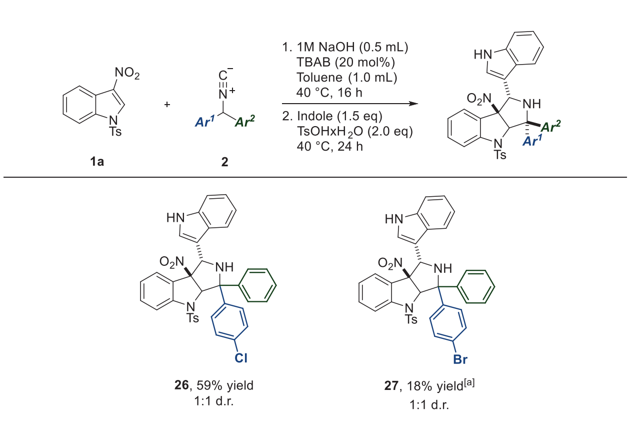
Based on the control experiments and previous literature reports, a reaction mechanism is proposed (Scheme 4).

In the first step, the C_α position of the isocyanide derivative is deprotonated under basic conditions. The resulting isocyanide anion then adds to the C2 position of the electron-deficient indole, forming intermediate **A**. This intermediate undergoes a 5-*endo*-dig cyclization to yield the imine product **3-IM**. Finally, arylation of the resulting imine under Brønsted acid conditions leads to the formation of the target products.

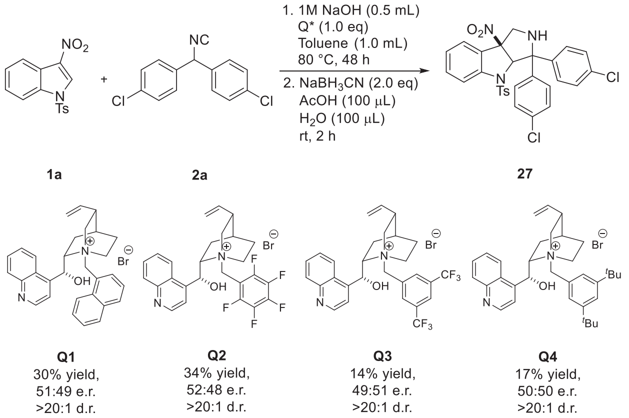
Finally, we explored the possibility of conducting the reaction under asymmetric conditions by replacing TBAB with cinchona alkaloid-derived phase-transfer catalysts. Since the enantiomeric information is introduced in the first step of the telescoped reaction and the alkylation step is diastereoselective, we reduced the imine in the second step during this screening (Scheme 5).

Employing the chiral phase-transfer catalyst **Q1** (20 mol%) under optimized reaction conditions resulted in only trace amounts of the dearomatized product **3-IM** after 48 h. A similar outcome was observed when the reaction temperature was raised to 80 °C and the catalyst loading was increased to 0.5

Table 4. Substrate scope III: Isocyanides.



a) De-aromatization step: 50 °C.



Scheme 5. Investigation of developed reaction with chiral catalysts.

equiv. When 1.0 equiv of the phase-transfer catalyst was used, product **3-IM** began to form, albeit with low conversion. To assess the enantioselectivity of the reaction, the reduction step was initiated after 48 h, despite incomplete dearomatization. Unfortunately, product **3** was isolated in low yield and as a racemate with all screened catalysts (**Q1–Q4**).

3. Conclusion

In conclusion, we developed an interrupted Barton–Zard reaction/Friedel–Crafts alkylation telescoped reaction for the synthesis of hexahydropyrrolo[3,4-b]indole skeletons bearing multiple aryl substituents. In the reaction between 3-nitroindoles and α,α-diaryl-substituted methyleneisocyanides, followed by the *in situ* addition of an aryl nucleophile, the target products were generally obtained in moderate to good yields, mostly as single diastereomers. While the reaction is tolerant of most electron-deficient indoles and nucleophiles, it is highly dependent on the structure of the isocyanide derivatives, with the dearomatization step proving to be the limiting step of the cascade. Investigations into potential side reactions are currently ongoing in our group.

4. Experimental Section

4.1. General Procedure for the Interrupted Barton–Zard/Friedel–Crafts Alkylation Telescoped Reaction

Selected 3-nitroindole (0.063 mmol) and isocyanide derivative (0.076 mmol) were dissolved in toluene (1 mL) at room temperature. 1 M NaOH (0.5 mL) and TBAB (0.013 mmol) were added, and the reaction mixture was stirred at 40 °C until completion (monitored by TLC, approx. 4 h). The water layer was removed, and selected nucleophile (0.095 mmol) and TsOHxH$_2$O (0.126 mmol) were added into the organic layer. The reaction was stirred at 40 °C until completion (monitored by TLC, approx. 24 h). The solvent was evaporated (the ^{1}H NMR of the crude reaction mixture was conducted at this point to confirm the diastereomeric ratio of the product), and the residue was directly purified by flash chromatography in petrol-ethyl acetate 5:1 unless otherwise indicated.

Supporting Information

The authors have cited additional references within the Supporting Information.[24] Supporting Information contains experimental procedures, characterization data, optimization of reaction conditions for the Friedel–Crafts alkylation step, and NMR spectra. The data that support the findings of this study (raw NMR data) are openly available in FULIR data at https://urn.nsk.hr/urn:nbn:hr:241:450511, reference number 450511.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are openly available in FULIR data at https://urn.nsk.hr/urn:nbn:hr:241:450511, reference number 450511.

Keywords: Dearomatization · Friedel–Crafts alkylation · Interrupted Barton–Zard reaction · Phase-transfer catalysis · Telescoped reaction

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