Dearomative cyclizations for the construction of polycyclic skeletons

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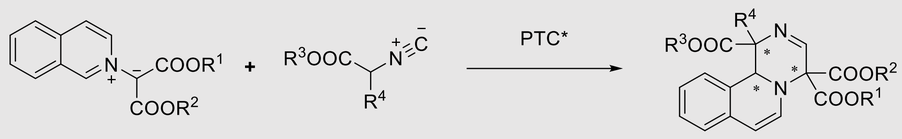
INTRODUCTION

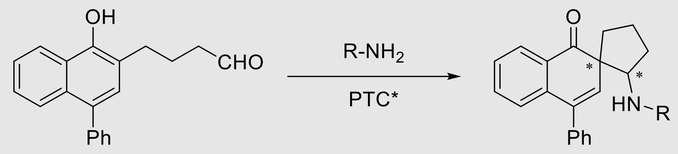
Among the top 200 small molecule drugs by retail sales in 2024, 71 of them contain polycyclic skeletons.[1] Usually, synthesis of these structures includes multiple-step routes and expensive starting materials. On the other hand, aromatic compounds as cheap and readily available bulk chemical feedstock provide direct access. Dearomatization reactions allow for escape from restrictions of aromaticity and forging of sophisticated three-dimensional molecular topologies. By taking inspiration from known drugs and bioactive natural products, organocatalytic asymmetric dearomatization (OCADA) reactions are being developed.

Azomethine ylides are readily employed in 1,3-dipolar cycloadditions for the construction of highly substituted heterocycles.[2] Usually, azomethine ylides are generated from α-iminoesters during the reaction course. On the other hand, their isoquinolinium derivatives are bench stable chemicals. In 2011, Carillo, Vicario et al. reported enantioselective [3+2] cycloaddition of isoquinolinium methylides with α,β-unsaturated carbonyl compounds.[3]

We aim to develop chiral PTC (phase-transfer catalyst) mediated OCADA [3+3] cycloaddition reactions between isoquinolinium methylides and α,α-disubstituted isocyanides for the construction of quinolizidine-type polycyclic skeletons (Scheme 1), as well as chiral PTC mediated OCADA spirocyclization of napthol derivatives (Scheme 2).



Scheme 1. Synthesis of quinolizidine-type polycycles through PTC mediated OCADA [3+3] cycloaddition

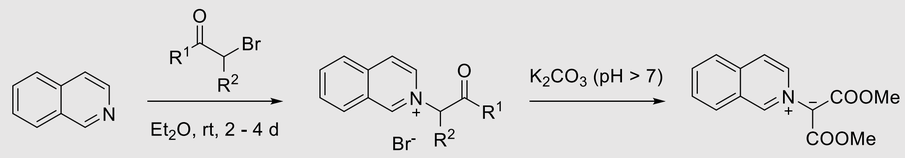


Scheme 2. PTC mediated spirocyclization of napthol aldehyde

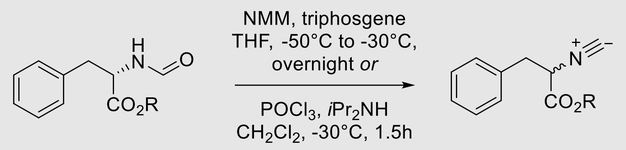
SYNTHESIS OF SUBSTRATES

Starting materials were prepared through known procedures. For [3+3] cycloaddition, isoquinolinium ylides were obtained by reaction of isoquinoline with α-halocarbonyl compounds, and subsequent deprotonation (Scheme 3). Isocyanides were obtained from the corresponding aminoacid formamide by dehydration (Scheme 4).

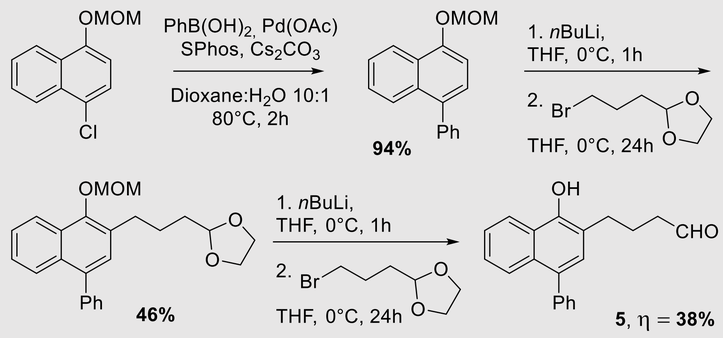
For spirocyclizations, the naphthol aldehyde was obtained starting from the corresponding MOM-protected 4-chloro-1-napthol, by Suzuki coupling to install a phenyl group, followed by *ortho*-lithiation, intoduction of protected aldehyde and removal of protecting groups (Scheme 5). A shorter aliphatic chain amine derivative was prepared by a smilar route starting from 4-chloro-1-napthol. The Suzuki product, obtained in the same manner, was subjected to *ortho*-formylation, followed by intoduction of a nitro alkene group through Knoevenagel reaction and reduction to aliphatic amine (Scheme 6). The final step yet to be performed is MOM deprotection.



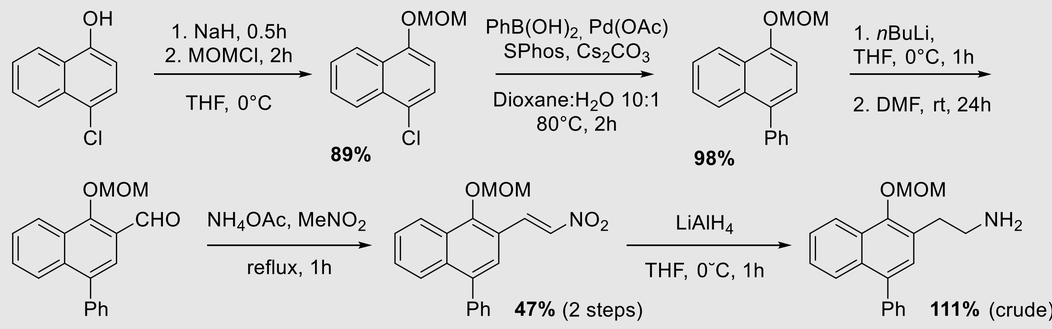
Scheme 3. Synthesis of isoquinolinium derivatives; R^1 = Ph, R^2 = H (**1**), **89%;** R^1 = OMe, R^2 = COOMe (**2**), **73%** (2 steps)



Scheme 4. Synthesis of isocyanides; R = Me (**3**), **80%,** R = ^{t}Bu (**4**), **95%**



Scheme 5. Synthesis of napthol aldehyde **5**

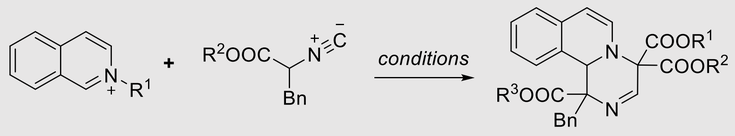


Scheme 6. Synthesis of protected napthol amine **6**

SCREENING OF REACTION CONDITIONS

Reactions of isoquinolinium derivatives (salt **1** and methylide **2**) with isocyanides (**3**,**4**) were carried out under condtitions summarized in Table 1. Different bases were used and reaction time and temperture were varied. Formation of desired product was not detected and starting isoquinilium compounds were recovered in large amounts. Isocyanides proved prone to decomposition in tested conditions. Formation of five membered ring products was observed and identified by NMR, though the exact structure could not be elucidated.

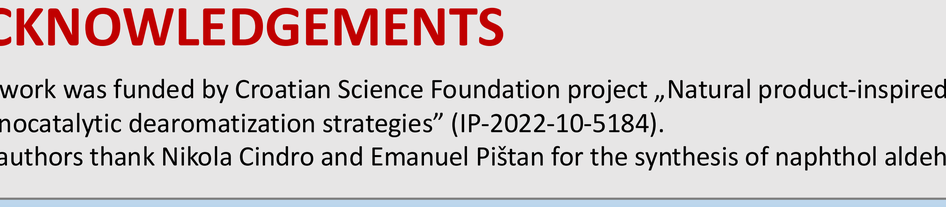
Table 1. [3+3] cycloaddition of isquinolinium derivatives and aminoacid ester isocyanides



Entry	R^1	R^2	Base	t / d	T / °C	Remark
1	$C^-(CO_2Me)_2$	^{t}Bu	Cs_2CO_3 (1.8 eq)	4 + 1	-10 to rt, 55	Isocyanide degraded 67% ylide recovered
2	$C^-(CO_2Me)_2$	Me	Cs_2CO_3 (3 eq)	4 + 1	0 to rt	1 eq of isocynide added after 4 d, 5-membered ring formation assumed by NMR
3	$C^-(CO_2Me)_2$	^{t}Bu	DBU (3 eq)	7	0 to rt	Similar to above
4	$C^-(CO_2Me)_2$	Me	50% NaOH (2.5 eq)	4	rt	Ester hydrolysis
5	$CH_2C(O)Ph; Br^-$	Me	Cs_2CO_3 (3 eq)	2 + 2	0	10 mol% TBAB added after 2 d, 67% salt/ylide recovered

Spirocyclization of naphthol aldehyde **5** in the presence of amines was carried out in acidic conditions (Table 2). In reactions performed in the presence of benzylamine and TsOH, in chlorinated solvents and at room temperature only starting material was recovered. Full conversion was achieved in toluene at elevated temperature, though only enamine formation was observed. Reactions carried out in the presence of more nucleophilic *p*-methoxyaniline yielded similar results. Synthesis of naphthol amine is in progress, which will be used in a similar reaction.

Table 2. Spirocyclization of naphthol aldehyde in presence of amines



Entry	Amine	Acid	Solvent (0.1M)	Temp. (°C)	Time (h)	Remark
1	benzylamine (1.2 eq)	TsOH (1.0 eq)	DCM	rt	48	only SM
2	benzylamine (1.2 eq)	TsOH (1.0 eq)	DCE	rt	48	only SM
3	benzylamine (1.2 eq)	TsOH (1.0 eq)	Toluene	rt	48	low conversion, **6** by NMR of RM
4	benzylamine (1.2 eq)	TsOH (1.0 eq)	Toluene	60	8	full conversion, **6** with several impurities
5	benzylamine (1.2 eq)	TsOH (1.0 eq)	Toluene	60	4+4	TsOH added after 4h, after complete conversion of SM to imine; only **6** with impurities
6	p-methoxyaniline (1.2 eq)	TsOH (1.0 eq)	Toluene	60	4	**6** with impurities by raw NMR
7	p-methoxyaniline (1.2 eq)	TsOH (0.2 eq)	Toluene	60	36	**6** with impurities by raw NMR
8	p-methoxyaniline (1.2 eq)	FFK (1.0 eq)	Toluene	60	16	**6** with impurities by raw NMR
9	p-methoxyaniline (1.2 eq)	TsOH (1.0 eq)	Toluene (0.5M)	60	4	mixture of products

CONCLUSIONS

- **Isoquinolinium salts and methylides, as well as α,α-disubstituted isocyanides and naphthol derivatives were synthesized**
- **Reactions of isoquinolinium derivatives with isocyanides were unsuccesful, though possible five-membered ring products were detected**
- **Spirocyclization of napthol aldehyde in the presence of amines yielded only enamine**
- **Spirocyclization of naphthol amine in the presence of aldehydes is in progress**

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[3] L. Gong, B. List, Chem. Commun. 2011, 47, 12313–12315.

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