Enantioselective synthesis of 3-substituted isoindolinones via chiral phase transfer catalyzed intramolecular aza-Michael reactions

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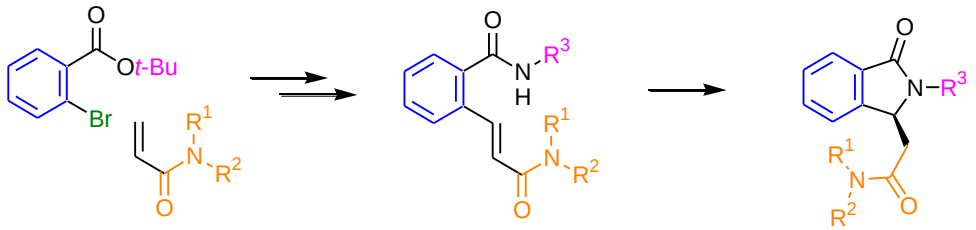
Abstract: Optically active isoindolinones are synthesized by asymmetric intramolecular aza-Michael reactions using cinchoninium phase-transfer organocatalysts. The resulting compounds are useful intermediates for the synthesis and development of benzazepine-receptor antagonists.



Keywords: *Organocatalysis, phase-transfer catalysis, aza-Michael, heterocycle, isoindolinone*

Introduction

2,3-Dihydro-1*H*-isoindol-1-ones (Isoindolinones) also called phthalimidines represent a class of bicyclic lactams which have attracted much attention from the scientific community due to the broad scope of their biological activities. [1] In particular, enantiopure compounds bearing a polysubstituted acetamido group at C-3 (Figure 1) have been extensively studied and play an important role as key targets for the pharmaceutical industry. Indeed, highly functionalized models, such as JM-1232 (**1**) [2] and DN-2327 (pazinaclone, **2**) [3] have been reported as benzodiazepinereceptor agonists for the treatment of anxiety.

1 (JM-1232) **2 (DN-2327)**

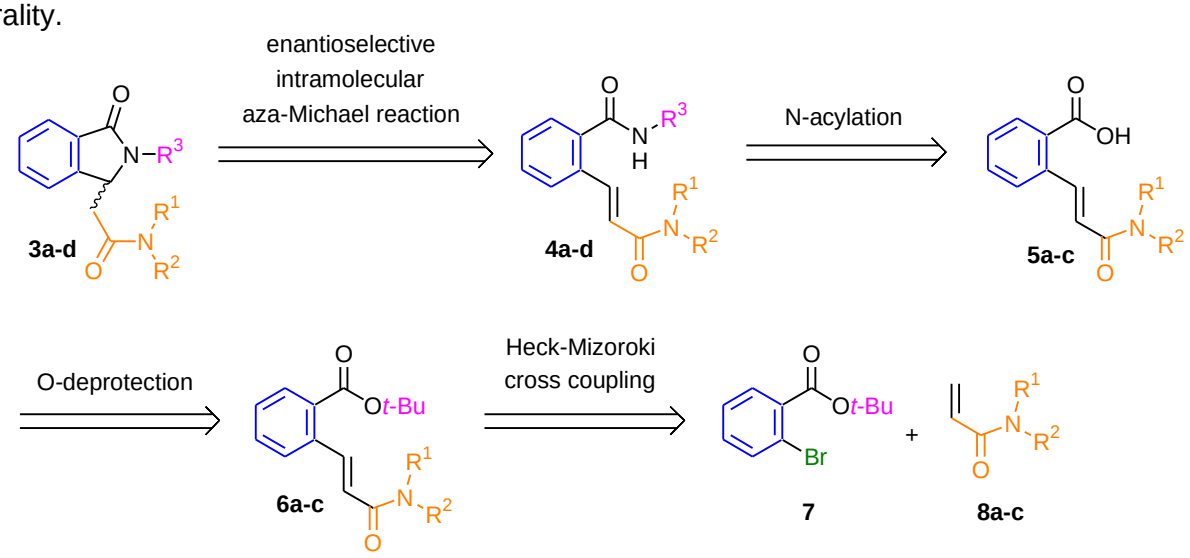
Figure 1. Examples of synthetic pharmacologicaly active chiral 3-(*N,N*-disubstituted)acetamido isoindolinones.

From these studies, the importance of the absolute configuration of the stereocenter on the pharmacological activity became clear.[2c] Consequently, the development of short, versatile and efficient procedures for the stereocontrolled preparation of these highly functionalized 3 substituted isoindolinones constitutes an area of current interest, and alternative methods are currently the object of intense synthetic endeavor. Organic chemists have at their disposal a variety of synthetic strategies for the racemic synthesis of 3-(N,N-disubstituted)acetamido isoindolinones mainly based upon metal-catalyzed tandem reactions. [4] To the best of our knowledge, in these bicyclic lactams, control of the stereogenic center α to the nitrogen has only been achieved through catalytic asymmetric reduction of a 3-alkoxycarbonylmethylene isoindolinone followed by a two-step ester–amide interconversion sequence. [5] The aza-Michael reaction involving the reaction of activated alkenes and amines was mainly applied in organic synthesis through the use of various metal or organic catalysts, [6] phase-transfer catalysis has been less studied for aza-Michael reactions. [7,8] Herein, we wish to disclose an alternative, efficient and new synthetic route to enantioenriched 3-(N,N-disubstituted)acetamido isoindolinones.

Results and Discussion

1. Our alternative strategie

Considering that most isoindolinones have been synthesized directly from *ortho*-halogenated benzamides through fast palladium-catalyzed tandem Heck and aza-Michael reactions, [4a–j] we concluded that the stereoselectivity of such a synthetic pathway would be difficult to control and the isolation of key reaction intermediates would be challenging.[4h,i] Hence, we envisioned a retrosynthetic strategy depicted in Scheme 1. Isoindolinones **3** may be available from an asymmetric intramolecular aza-Michael reaction of benzamides **4** by the construction of the lactam ring system and the concomitant control of the stereogenic center at C3. The stereoselectivity of the intramolecular aza-Michael reaction should be controlled by the catalyst chirality.

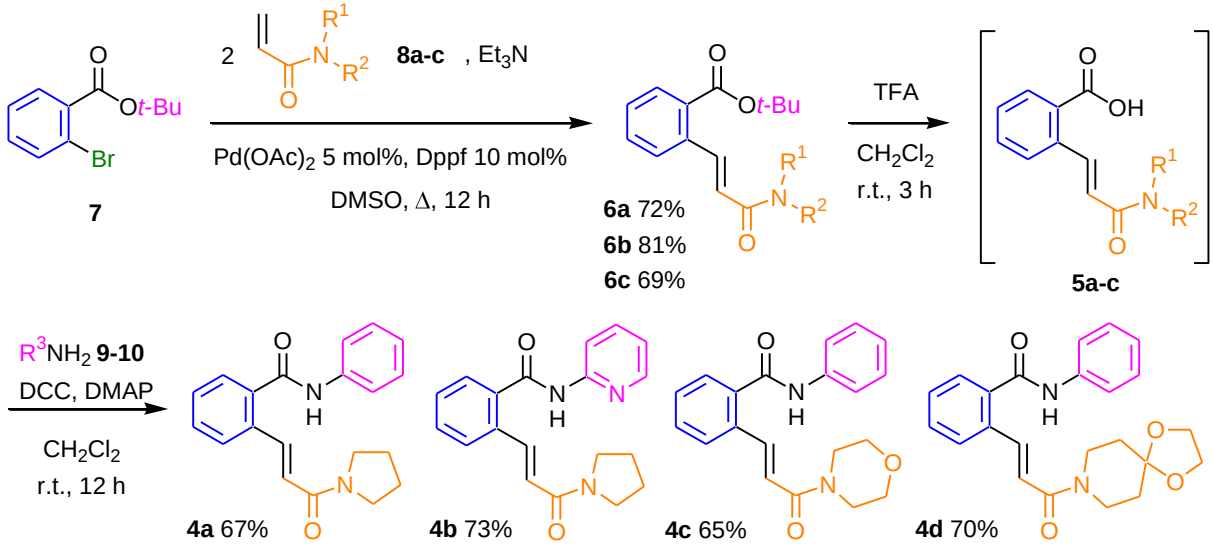


Scheme 1. Retrosynthetic analysis of chiral 3-substituted isoindolinones.

The required benzamides **4** should be easily obtained from the corresponding unsaturated benzoic acids **5** by coupling with an array of primary amines. The acid **5** should, in turn, be readily prepared through a two-step sequence involving a cross-coupling Heck type reaction between 2-bromoester **7** and acrylamides **8** followed by deprotection of the *tert*-butyl esters **6**.

2. Elaboration of parent unsaturated amides 4a-d

The new synthetic route required the preliminary elaboration of the unsaturated *tert*-butyl benzoic acid esters **6a–c**, which were readily prepared through a palladium-catalyzed Heck cross-coupling between aryl bromide **7** and various acrylamides **8a–c** (Scheme 2).

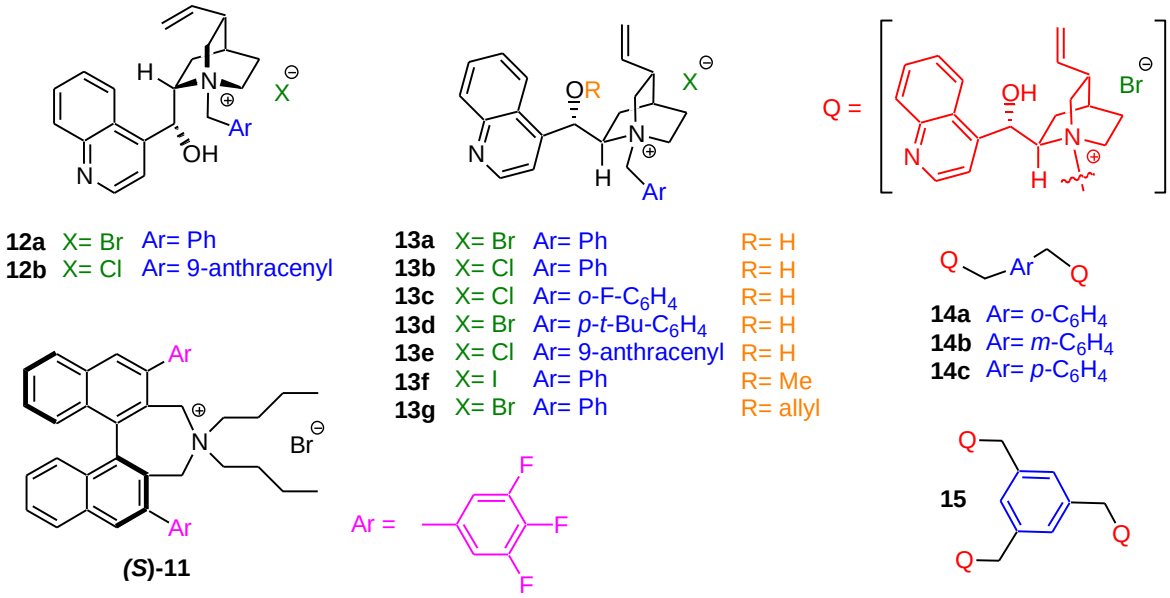


Scheme 2. Synthesis of 3-substituted isoindolinone precursors

Removal of the *tert*-butyl protecting group was then achieved by treatment with trifluoroacetic acid to furnish benzoic acids **5a–c**, which were then engaged in the next step without further purification. Coupling of these highly conjugated carboxylic acids with aniline **9** and 2-aminopyridine **10** finally delivered the required parent amides **4a–d**. It was worth noting that this coupling reaction led directly to the corresponding cyclized products **3** when acrylamide fragments were replaced by conjugated esters.

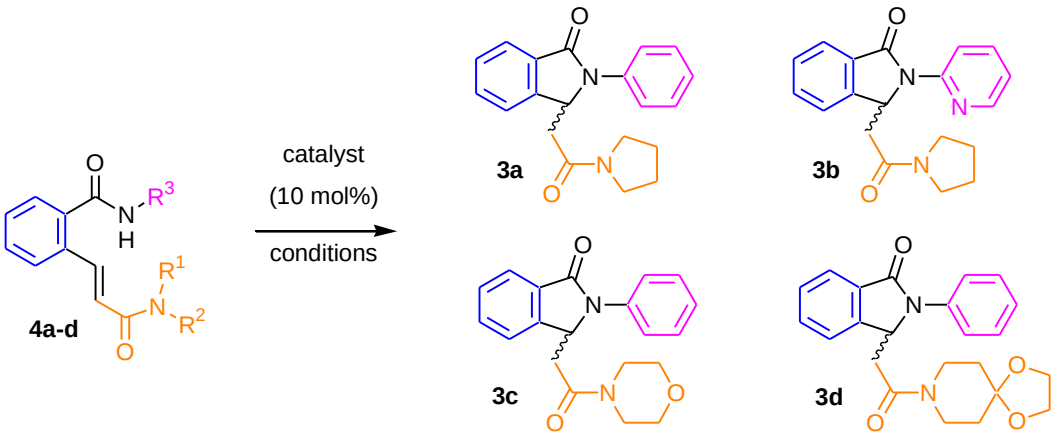
3. Asymmetric intramolecular aza-Michael reaction of amides 4a-d. Access to enantioenriched 3-substituted isoindolinones 3a-d.

The asymmetric intramolecular aza-Michael reactions of substrates **4a–d** (scheme 4) was studied by screening various phase transfer catalysts (Scheme 3) and reaction conditions (Table 1). Because some aza-Michael reactions have been shown to proceed without the use of any catalyst or additional reagent, [6e,9] we first performed a number of control experiments. Conducting the reaction with reagent **4a** led to product **3a** by using a base such as Cs_2CO_3, in toluene (entry 1). Using the same reaction conditions, Maruoka catalyst (*S*)-**11** and cinchoninium salt **13a** were shown to afford **3a** in high conversions with 20 and 21% enantiomeric excess (ee), respectively (entries 2 and 5), whereas poor asymmetric induction was achieved by the use of cinchonidinium salt **12a** or **12b** (entries 3 and 4). The use of cinchoninium salt **13a** in combination with other bases (entries 6–8) or solvents (entries 9 and 10) did not improve the initially obtained ee value (entry 5). The bromide couteranion of **13a** was shown to be preferred to the chloride of **13b** (entries 5 and 11); other anions like iodide and tetrafluoroborate were tried by ion exchange in situ but no improvement in the ee value arose from these attempts (entries 12 and 13). Finally, the use of catalyst **13a** at 0 °C resulted in complete loss of enantiomeric excess in the product **3a** (entry 14).



Scheme 3. Phase-transfer catalysts applied to the intramolecular aza-Michael reactions of reagents **4a-d**.

The effect of substitution of the benzyl fragment of cinchoninium **13a** on the reaction was then studied. Whereas an *ortho*-fluoro substituent led to loss of asymmetric induction (entry 15), a *para*-positioned *tert*-butyl fragment had no effect on the selectivity of the reaction (entry 16). The change from a benzyl to an anthracenyl group resulted in complete loss of enantioselection (entry 17). Disappointing results were also obtained from the functionalization of the alcohol fragment from cinchoninium **13a** (entries 18–20). Whereas an allyl function did not change the course of the reaction, provided Cs_2CO_3 was used as a base, a methyl substituent led to complete loss of asymmetric induction. Because we were unable to improve catalyst **13a** by scaffold modification, we decided to investigate oligomeric cinchoninium salts [7b,10] based on **13a**. Whereas, dimeric catalysts **14a** and **14c** afforded **3a** in lower ee than **13a** (entries 5, 21 and 23), *meta*-substituted cinchoninium salt **14b** led to product **3a** in a 45% ee (entry 22). Encouraged by this result, we prepared trimeric cinchoninium catalyst **15** and allowed it to react with **4a**. We were glad to obtain isoindolinone **3a** in 95% conversion (78% isolated yield) and 76% ee (entry 24). Whereas the use of K_2CO_3 did not allow any reaction (entry 25), changing the temperature (entry 26) or solvent (entry 27) led to a decrease of **3a** enantioselectivity using catalyst **15**. Reagent **4b**, bearing a 2-pyridyl substituent, led to product **3b** in 72% yield but no enantioselectivity was observed (entry 28). Asymmetric aza-Michael reactions of benzamide substrates **4c–d** worked well using catalyst **15**, although enantioselectivities of **3c–d** were lower, with ee values around 60% (entries 29 and 30).



Scheme 4. Synthesis of 3-substituted enantioenriched isoindolinones **3a-d**.

Entry	Reagent	Catalyst	Base	Solvent	Temp (°C)	Yield (%)[b]	E.e (%)[c]
1	**4a**	**none**	Cs_2CO_3	Toluene	r.t.	74	0
2	**4a**	**(*S*)-11**	Cs_2CO_3	Toluene	0	77	20
3	**4a**	**12a**	Cs_2CO_3	Toluene	r.t.	73	3
4	**4a**	**12b**	Cs_2CO_3	Toluene	r.t.	70	8
5[d]	**4a**	**13a**	Cs_2CO_3	Toluene	r.t.	75	21
6	**4a**	**13a**	K_3PO_4	Toluene	r.t.	19	-
7	**4a**	**13a**	DBU	Toluene	r.t.	78	6
8[e]	**4a**	**13a**	KOH 50%	Toluene	r.t.	80	4
9	**4a**	**13a**	Cs_2CO_3	THF	r.t.	76	7
10	**4a**	**13a**	Cs_2CO_3	CH_2Cl_2	r.t.	73	3
11	**4a**	**13b**	Cs_2CO_3	Toluene	r.t.	75	0
12[e]	**4a**	**13a**	Cs_2CO_3	Toluene	r.t.	78	18
13[f]	**4a**	**13a**	Cs_2CO_3	Toluene	r.t.	72	21
14	**4a**	**13a**	Cs_2CO_3	Toluene	0	75	0
15[g,h]	**4a**	**13c**	Cs_2CO_3	Toluene	r.t.	74	0
16	**4a**	**13d**	Cs_2CO_3	Toluene	r.t.	77	20
17	**4a**	**13e**	Cs_2CO_3	Toluene	r.t.	73	0
18	**4a**	**13f**	Cs_2CO_3	Toluene	r.t.	80	0
19	**4a**	**13g**	Cs_2CO_3	Toluene	r.t.	74	21
20[g]	**4a**	**13g**	KOH 50%	Toluene	r.t.	71	6
21	**4a**	**14a**	Cs_2CO_3	Toluene	r.t.	79	17
22	**4a**	**14b**	Cs_2CO_3	Toluene	r.t.	75	45
23	**4a**	**14c**	Cs_2CO_3	Toluene	r.t.	71	12
24	**4a**	**15**	Cs_2CO_3	Toluene	r.t.	78	76
25	**4b**	**15**	K_2CO_3	Toluene	r.t.	0	-
26	**4a**	**15**	Cs_2CO_3	Toluene	-5	69	45
27	**4a**	**15**	Cs_2CO_3	CH_2Cl_2	r.t.	73	2
28	**4a**	**15**	Cs_2CO_3	Toluene	r.t.	72	0
29	**4c**	**15**	Cs_2CO_3	Toluene	r.t.	80	59
30	**4d**	**15**	Cs_2CO_3	Toluene	r.t.	75	61

[a] Reaction time : 24h. [b] Isolated yield after purification by flash chromatography. [c] measured by HPLC (Daicel Chiralpak AD CSP, Hexane-*i*PrOH, 7:3; 20 °C, 0.5 ml/min, 275 nm. [d] no reaction after 6 h. [e] with 10 mol% NaI. [f] with 10 mol% $NaBF_4$. [g] same result using Toluene/$CHCl_3$ (7/3). [h] same result using KOH 50% aq. as base.

Table 1 Phase transfer-Catalyzed intramolecular Aza-Michael reaction of **4a-d**[a]

Conclusion

In summary, we have developed a new synthetic route to optically active isoindolinones, which are useful intermediates for the synthesis and development of benzodiazepine- receptor agonists.To access such isoindolinones, asymmetric intramolecular aza Michael reactions proved to be a valuable synthetic route provided selected oligomeric cinchoninium salts were used as phase-transfer catalysts. Further results and improvements related to this project will be reported in due course.

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