Chiral phase-transfer catalyzed intramolecular aza-Michael reactions for the asymmetric synthesis of isoindolinones

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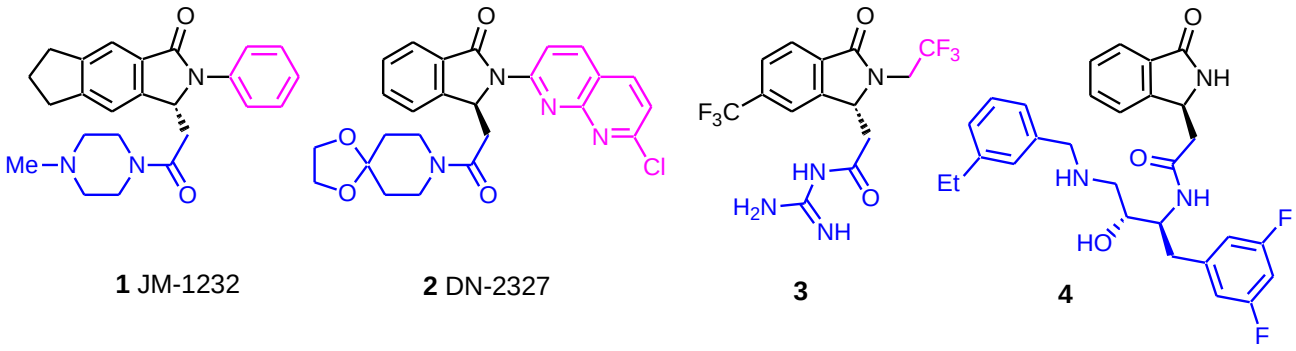
Abstract: Asymmetric intramolecular aza-Michael reactions catalyzed by cinchoninium phase-transfer organocatalysts are used for the synthesis of optically active isoindolinones. Selected oligomeric cinchoninium salts proved to be efficient and selective catalysts for the intramolecular addition of alkenylated benzamide substrates. The resulting compounds are useful intermediates for the synthesis and development of benzodiazepine-receptor agonists.

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

Introduction

Over the past decade, the isoindolinone ring system has emerged as a valuable pharmacophore due to the physiological and chemotherapeutic properties of many of its derivatives. [1] In particular, enantiopure compounds bearing at C-3 a polysubstituted acetamido group (Fig. 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 benzodiazepine-receptor agonists for treatment of anxiety. Isoindolinone **3** bearing an acetylguanidine group has been studied as a NHE1 inhibitor [4] whereas *N*-(3-amino-2-hydroxypropyl) substituted alkanamides such compound **4** have been reported as inhibitor of the β-secretase enzyme for treating Alzheimer's disease. [5] From these studies, the importance of the absolute configuration of the stereocenter on the pharmacological activity emerged clearly. [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 intensive synthetic endeavour.



1 JM-1232 **2** DN-2327 **3** **4**

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

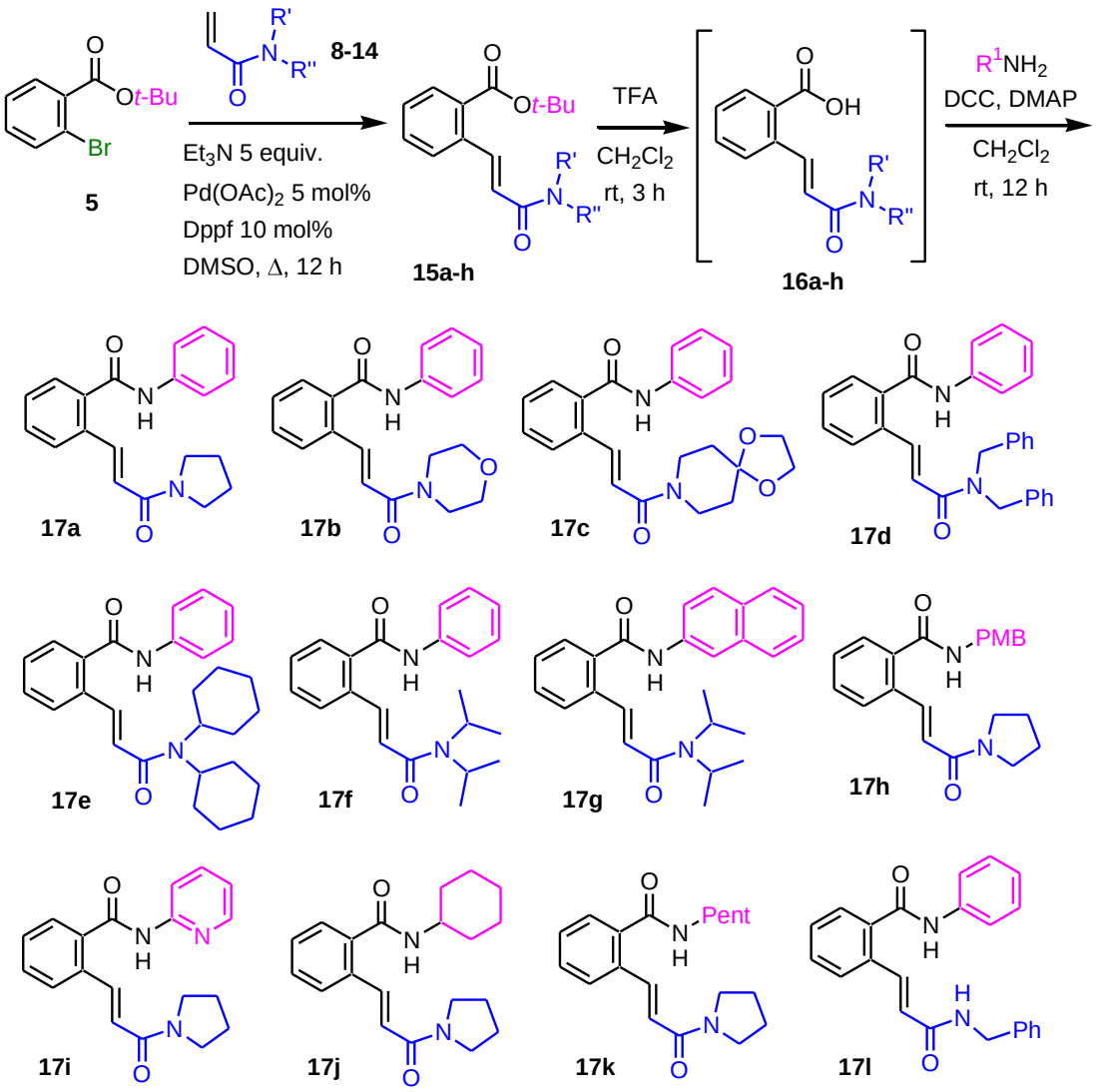
Organic chemists have at their disposal a variety of synthetic strategies for the racemic synthesis of 3-(*N*,*N*-disubstituted)acetamido isoindolinones mainly based upon metal-catalysed tandem reactions. [6] Because most of isoindolinones have been synthesised directly from *ortho*-halogenated benzamides through a fast palladium catalysed tandem Heck and aza-Michael reaction, [6a-j] the stereoselectivity of such a synthetic pathway could be hardly controlled and isolation of key reaction intermediates was rather difficult. [6h,l]

Following our separated but ongoing interests in the synthesis of isoindolinones [7d,8c,g] and aza-Michael reactions, [7] we have envisaged a new reaction pathway which could afford isoindolinones from an asymmetric intramolecular aza-Michael reaction of benzamides 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 could be controlled by the catalyst chirality. The aza-Michael reaction involving the reaction of activated alkenes with amines was largely applied in organic synthesis. [8-10] On the one hand, chiral auxiliaries or substrates were used for diastereo- or enantiocontrolled aza-Michael reactions. On the other hand, various organic or metal catalysts could be applied for asymmetric aza-Michael reactions. [8-10] Whereas Brønsted acids, bases, primary or secondary amines were largely used as chiral organocatalysts, [8,9] phase-transfer catalysis has been less studied for asymmetric aza-Michael reactions. [11,12] Following our preliminary communication, [12m] we wish to disclose herein a full and understandable study on an alternative, efficient and new synthetic route for enantioenriched 3-(*N*,*N*-disubstituted)acetamido isoindolinones.

Results and Discussion

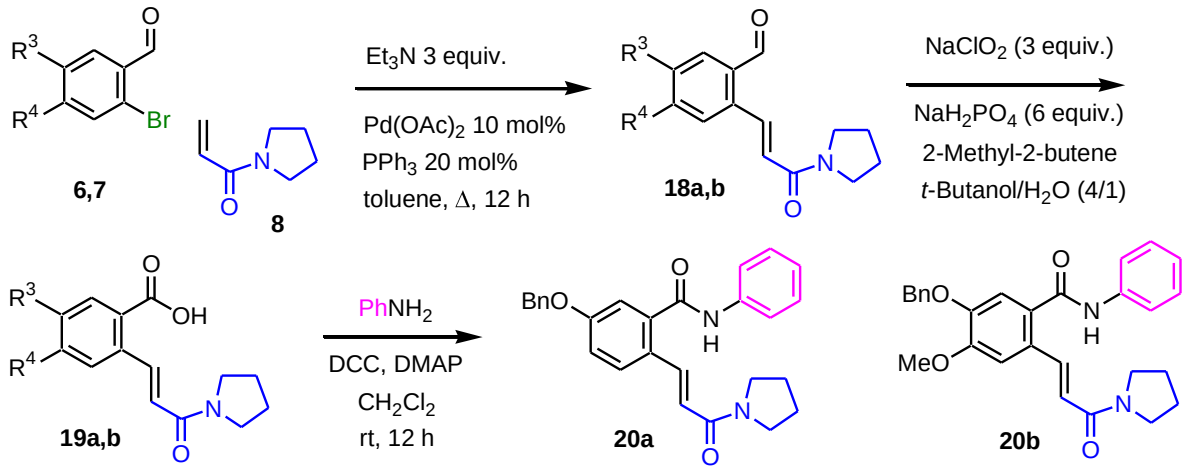
1. Synthesis of alkenylated benzamide substrates

In order to perform the foreseen asymmetric intramolecular aza-Michael reaction, alkenylated benzamide substrates were designed and synthesized. Depending on the reagent substituents, different synthetic pathways have to be applied. A first synthetic route implied the preliminary elaboration of the unsaturated *t*-butyl benzoic acid esters **15a-h** through a palladium-catalysed Heck cross coupling between aryl bromide **5** and various acrylamides **8-14** (Scheme 1). Removal of the *t*-butyl protecting group was then achieved by treatment with trifluoroacetic acid to furnish the benzoic acids **16a-h** which could be directly used for the next step without any purification. Coupling of these highly conjugated carboxylic acids with several primary amines finally delivered the required parent amides **17a-l** in good yields.



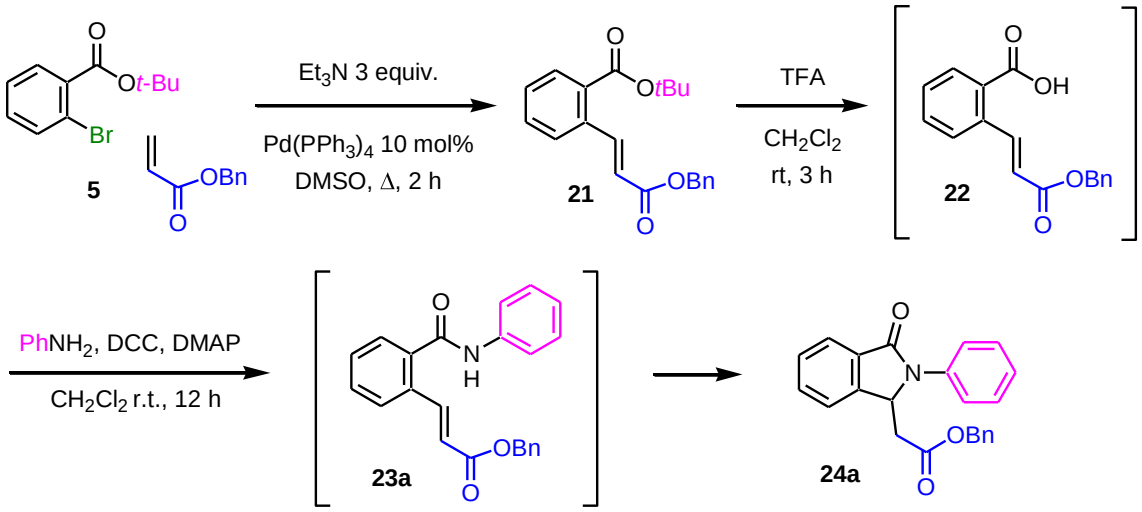
Scheme 1. Synthesis of benzamides **17a-l**

Reagents **20a,b** were synthesised through a Heck cross coupling between aldehydes **6-7** and acrylamide **8** in order to avoid side reactions. Subsequent oxidation of **18a,b** led to carboxylic acids **19a,b** which were directly coupled with aniline to afford the desired amides **20a,b** (Scheme 2).



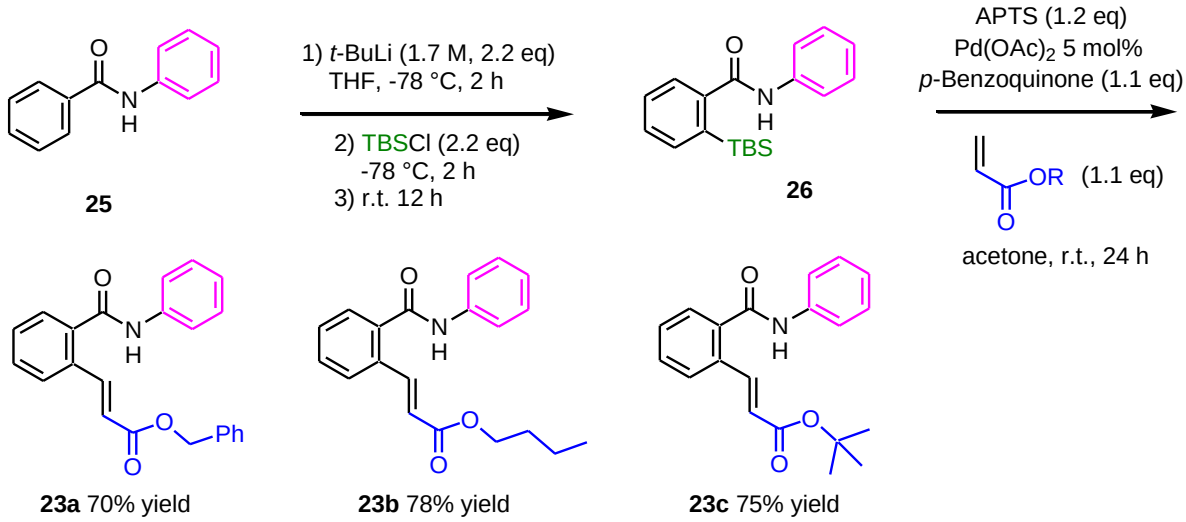
Scheme 2. Synthesis of benzamides **20a-b**

However, although acid **22** could be readily prepared from reagent **5** and ester **21**, its coupling with aniline directly led to the corresponding cyclized products **24a** (scheme 3).



Scheme 3. Synthesis of benzamide **23a**

Hence, benzamides derivatives **23a-c** had to be prepared using an alternative synthetic pathway from *N*-phenylbenzamide **25** (Scheme 4). First, an *ortho*-lithiation step followed by a trapping with TBDMSCl reagent led to the intermediate 2-(*t*-butyldimethylsilyl)-*N*-phenylbenzamide **26**. Second, a catalytic amide-directed palladadesilylation–alkenylation offered the desired benzamides **23a-c** in mild conditions and good yields. [13]



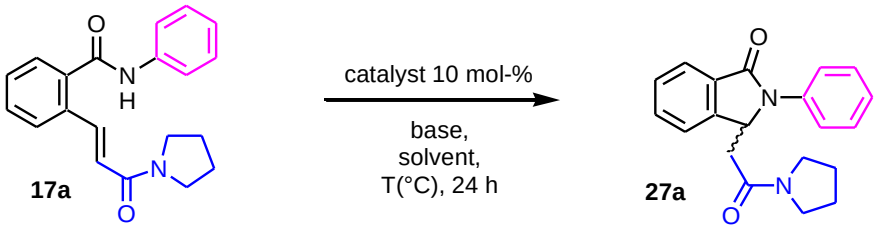
Scheme 4. Synthesis of benzamides **23a-c**

2. Asymmetric intramolecular aza-Michael reaction.

The asymmetric intramolecular aza-Michael reaction of substrate **17a** was first studied as model to screen various privileged phase-transfer catalysts and optimize the reaction conditions (Table 1 and Figure 2). Because some aza-Michael reactions were shown to be achieved without the use of any catalyst or additional reagent, [7,8f,14] we performed first control experiments. The reaction of reagent **17a** led to product **27a** solely by using a base like Cs_2CO_3, in toluene (entry 1). Within the same reaction conditions, Maruoka catalyst (*S*)-**28** afforded **27a** in high yield with 20% enantiomeric excess (ee) (entry 2). The use of cinchoninium salt **30a** as a catalyst led to similar results (entry 5) whereas poor asymmetric

induction was achieved by the use of cinchonidinium salt **29a**, Corey catalyst **29b** or quinidinium salt **31** (entries 3, 4, 6). The use of cinchoninium salt **30a** in combination with other bases (entries 7-9) or solvents (entries 10, 11) didn't improve the ee initially obtained (entry 5). In order to check if bromide was the best couteranion for **30a**, iodide and tetrafluoroborate anions were tried by *in-situ* ion exchange but no ee improvement arose from these attempts (entries 13, 14). In addition, cinchoninium salt **30b** bearing a chloride anion proved to be unselective (entry 12). Finally, the use of catalyst **30a** at 0 °C resulted also in a complete loss of **27a** enantiomeric excess (entry 15).

Table 1. First catalytic attempts



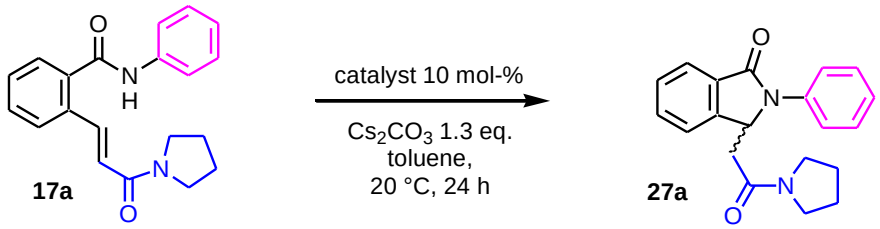
Entry	Cat.	Base	Solvent	T (°C)	Yield (%)[a]	Ee (%)[b]
1	-	Cs_2CO_3	toluene	20	74	0
2	**28**	Cs_2CO_3	toluene	0	77	20
3	**29a**	Cs_2CO_3	toluene	20	73	3
4	**29b**	Cs_2CO_3	toluene	20	70	8
5[c]	**30a**	Cs_2CO_3	toluene	20	75	21
6	**31**	Cs_2CO_3	toluene	20	75	13
7	**30a**	K_3PO_4	toluene	20	19	-
8	**30a**	DBU	toluene	20	78	6
9	**30a**	KOH 50%	toluene	20	80	4
10	**30a**	Cs_2CO_3	THF	20	76	7
11	**30a**	Cs_2CO_3	CH_2Cl_2	20	73	3
12	**30b**	Cs_2CO_3	toluene	20	75	0
13[d]	**30a**	Cs_2CO_3	toluene	20	78	18
14[e]	**30a**	Cs_2CO_3	toluene	20	72	21
15	**30a**	Cs_2CO_3	toluene	0	75	0

[a] Isolated yield. [b] measured by HPLC. [c] no reaction after 6 hours. [d] with 10 mol-% NaI. [e] with 10 mol-% $NaBF_4$

We next screened various mono- and polynuclear organocatalysts based on a cinchonine core for the aza-Michael reaction of benzamide **17a** (Table 2, Figure 2). The substitution effect of the benzyl fragment was the first modification of cinchoninium catalyst **30a** studied. Whereas an *ortho*-fluoro substituent led to a loss of asymmetric induction (entries 1, 2), a *para*-*t*-butyl fragment had no effect on the selectivity of the reaction (entry 3). The change from a benzyl- to an anthracenyl group resulted in complete loss of enantioselection (entry 4). Disappointing results were also obtained for the functionalization of the alcohol fragment from cinchoninium **30a**. Whereas an allyl function didn't change the course of the reaction provided (entries 6-7), a methyl substituent led to complete loss of the asymmetric induction (entry 5).

In order to improve the ability of the alcohol fragment to form hydrogen bonds with the substrate, carbamate, urea and thiourea catalysts **32a-c** were investigated. Though the use of carbamate **32a** slightly improved the ee, catalysts **32b-c** were not selective (entries 8-10). Because catalyst **30a** could not be improved by any scaffold modification, we decided to investigate oligomeric cinchoninium salts [11b,15] based on **30a**. Dimeric catalysts **33a-c** build on a benzene core were first investigated. Whereas salts **33a,c** afforded **27a** in lower ee than salt **30a** (entries 1, 11, 13), *meta*-substituted cinchoninium salt **33b** led to product **27a** in a 45% ee (entry 12). The used of dimeric catalysts **34a,b** and **35** based on naphtyl and anthracenyl cores resulted in lower enantioselectivities (entries 14-16) and only a dimeric catalyst based on a biphenyl core could afford product **27a** in a 41% ee (entries 17-19).

Table 2. Screening of various catalysts for the phase transfer catalyzed intramolecular Aza-Michael reaction of benzamide **17a**



Entry	Catalyst	Yield (%)[a]	E.e (%)[b]
1[c]	**30a**	75	21
2[c, d]	**30c**	74	0
3[e]	**30d**	77	20
4	**30e**	73	0
5	**30f**	80	0
6	**30g**	74	21
7[c, f]	**30g**	71	6
8	**32a**	78	23
9	**32b**	82	5
10	**32c**	79	8
11	**33a**	79	17
12	**33b**	75	45
13	**33c**	71	12
14	**34a**	82	32
15	**34b**	78	32
16	**35**	70	10
17	**36a**	75	6
18	**36b**	76	41
19	**36c**	100	6
20	**37a**	78	76
21	**38**	80	32

[a] isolated yield. [b] measured by HPLC. [c] same result using Toluene/$CHCl_3$ (7/3). [d] same result using KOH 50% aq. as base. [e] same result 30 mol-% of catalyst. [f] using KOH 50% aq.

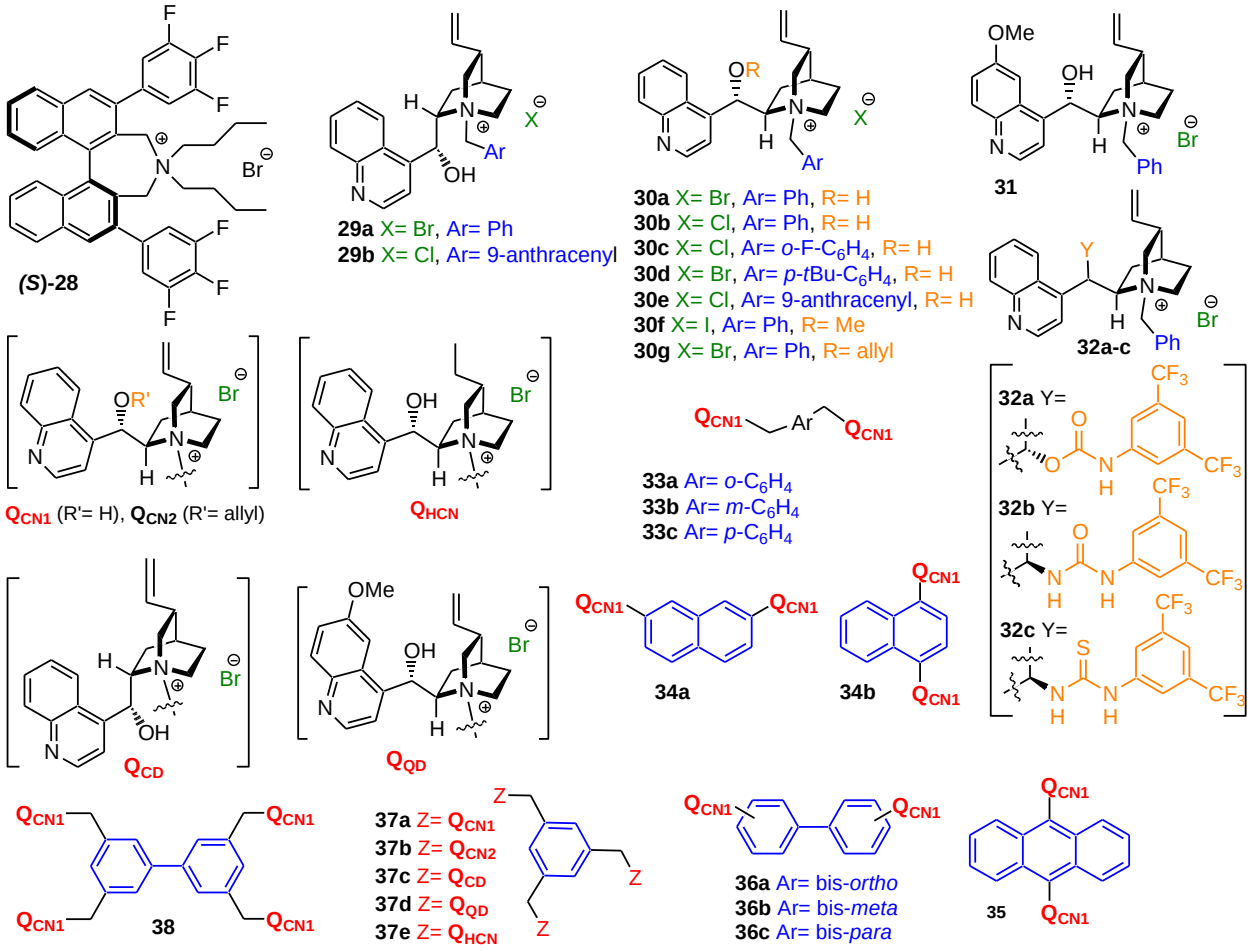
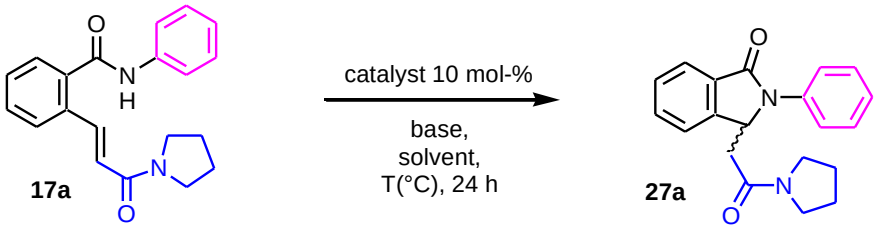


Figure 2. Organo-catalysts used in this study

Catalyst **37a** was optimized for the aza-Michael reaction of benzamide **17a** by trying some scaffold modifications as well as different reaction conditions (Table 3, Figure 2). Several trimeric catalysts were prepared using cinchonidine, quinidine and reduced cinchonine. However, if all attempts afforded **27a** in good yields, lower ee were obtained and salt **37a** remained the catalyst of choice (entries 1-5). Regarding the reaction conditions, we noticed the use of other bases didn't improve the reaction outcome. K_2CO_3 didn't allow any reaction and aqueous KOH led to lower ee (entries 6, 7). Moreover, the use of an additional amount of Triton X surfactant resulted in a complete loss of enantioselection (entry 8). Changing the solvent or the catalyst loading led to a decrease of **27a** enantioselectivity (entries 9, 10, 12). Finally, the use of catalyst **37a** at 50 °C implied no change of yield and ee (entries 1, 11).

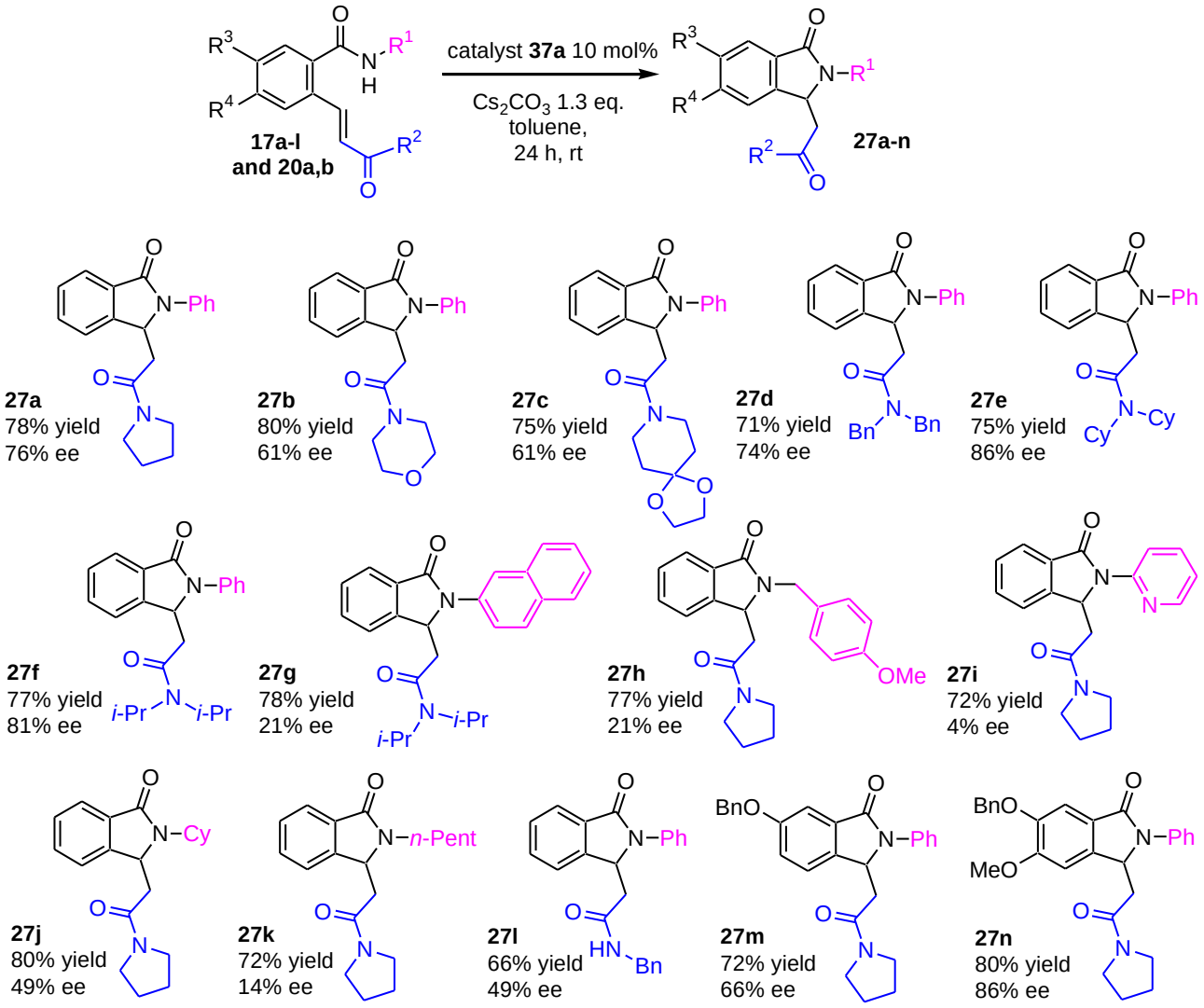
Table 3. Optimization of trimeric cinchoninium catalyst **37a-e**



Entry	Cat.	Base	Solvent	T (°C)	Yield (%)[a]	Ee (%)[b]
1	**37a**	Cs_2CO_3	Toluene	20	78	76
2	**37b**	Cs_2CO_3	Toluene	20	79	10
3	**37c**	Cs_2CO_3	Toluene	20	83	29
4	**37d**	Cs_2CO_3	Toluene	20	77	32
5	**37e**	Cs_2CO_3	Toluene	20	78	35
6	**37a**	K_2CO_3	Toluene	20	0	-
7	**37a**	KOH 50%	Toluene	20	73	30
8[c]	**37a**	KOH 50%	Toluene	20	65	0
9	**37a**	Cs_2CO_3	DMF	20.	75	5
10	**37a**	Cs_2CO_3	CH_2Cl_2	20	73	2
11	**37a**	Cs_2CO_3	Toluene	50	79	74
12[d]	**37a**	Cs_2CO_3	Toluene	20	72	18

[a] isolated yield. [b] measured by HPLC. [c] with 5 mol-% of Triton X. [d] with 30 mol-% of catalyst.

In order to explore the substrate scope of this phase-transfer catalysed intramolecular aza-Michael reaction, various benzamides were allowed to react in the presence of catalyst **37a** using selected reaction conditions (Scheme 5). On the whole, the reactions proceeded smoothly affording products in good yields without any substituent effect. Regarding the variation in enantioselectivity, several trends could be observed. Considering first the R^2 substituent, benzamide substrates **17b,c** with cyclic amines reacted well though enantioselectivities of **27b,c** were lower with 61% ee. At the exception of reagent **17g** substituted with bulky isopropyl groups, the use of non-cyclic amines as R^2 substituent afforded products **27d,e,f** in equivalent to higher enantioselectivities. When R^2 was an *O*-alkyl group, the resulting isoindolinones could be isolated in good yields but poor enantiomeric excesses were obtained (see Scheme 4). Regarding the substituent R^1, the reactivity of reagents **17g-k** proved the nature of R^1 was critical in order to get a good enantioselectivity (Scheme 5, products **27g-k**). Phenyl substituent had to be preferred to 2-naphtyl, benzyl, 2-pyridyl or alkyl substituents. Finally, whereas the reactivity of substrates **20a,b** proved the enantioselectivity was much less dependent on the nature of substituents R^3 and R^4 (products **27m,n**), the reaction of reagents **17d** and **17l** confirmed tertiary amides were the best substituents on the Michael acceptor in order to reach a high enantioselection (products **27d,l**).



Scheme 5. Scope of amide substrates **27**

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. However, specific substitution patterns on the amide nitrogen and to a lesser extent on the Michael-acceptor were necessary in order to reach high enantioselectivities. Further developments related to that project will be reported in the future.

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