

Enantioenriched Isoindolinones from Chiral Phase-Transfer-Catalyzed Intramolecular Aza-Michael Reactions

Romain Sallio,^{a,b} Stéphane Lebrun,^{a,b} Nadège Schifano-Faux,^{a,c} Jean-François Goossens,^{a,c} Francine Agbossou-Niedercorn,^{a,d,e} Eric Deniau,^{*a,b} Christophe Michon^{*a,d,e}

^a Université Lille Nord de France, 59000 Lille, France

^b Université Lille 1, Laboratoire de Chimie Organique Physique, EA CMF 4478, Bâtiment C3(2), 59655 Villeneuve d'Ascq Cedex, France
Fax +33(3)20436585; E-mail: Eric.Deniau@univ-lille1.fr

^c UDSL, EA 4481, 59000 Lille, France

^d CNRS, UCCS UMR 8181, 59655 Villeneuve d'Ascq, France

^e ENSCL, CCM-CCCF, Bât C7, CS 90108, 59652, Villeneuve d'Ascq, France
E-mail: Christophe.Michon@ensc-lille.fr

Received: 22.05.2013; Accepted after revision: 01.07.2013

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 benzodiazepine-receptor agonists.

Key words: organocatalysis, phase-transfer catalysis, aza-Michael, heterocycles, isoindolinone

2,3-Dihydro-1*H*-isoindol-1-ones (isoindolinones), also called phthalimidines, represent a class of bicyclic lactams that have attracted much attention from the scientific community due to the broad scope of their biological activities.¹

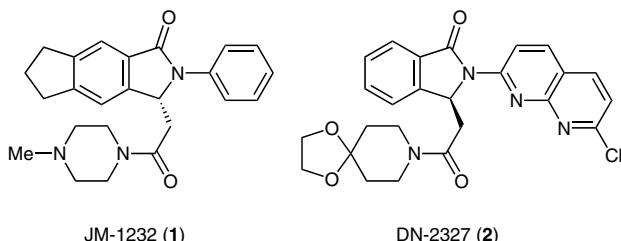


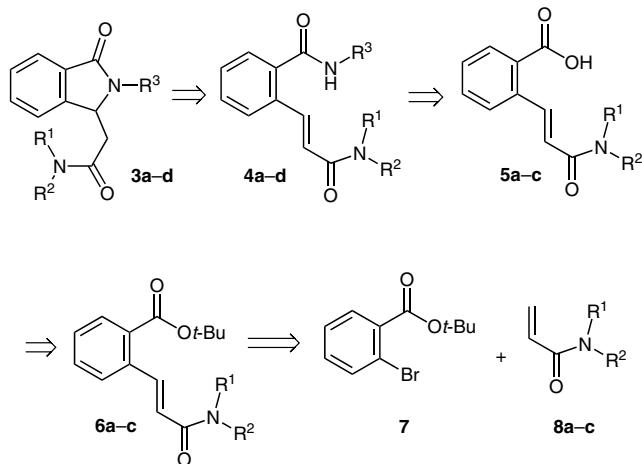
Figure 1 Examples of synthetic pharmacologically active chiral 3-(N,N-disubstituted)acetamido isoindolinones

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 benzodiazepine-receptor agonists for the treatment of anxiety. 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 prepara-

tion 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.

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.

The required benzamides **4** should be easily obtained from the corresponding unsaturated benzoic acids **5** by coupling with an array of secondary 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**. The new synthetic route required the preliminary elaboration of the unsatu-



Scheme 1 Retrosynthetic analysis of chiral 3-substituted isoindolinones

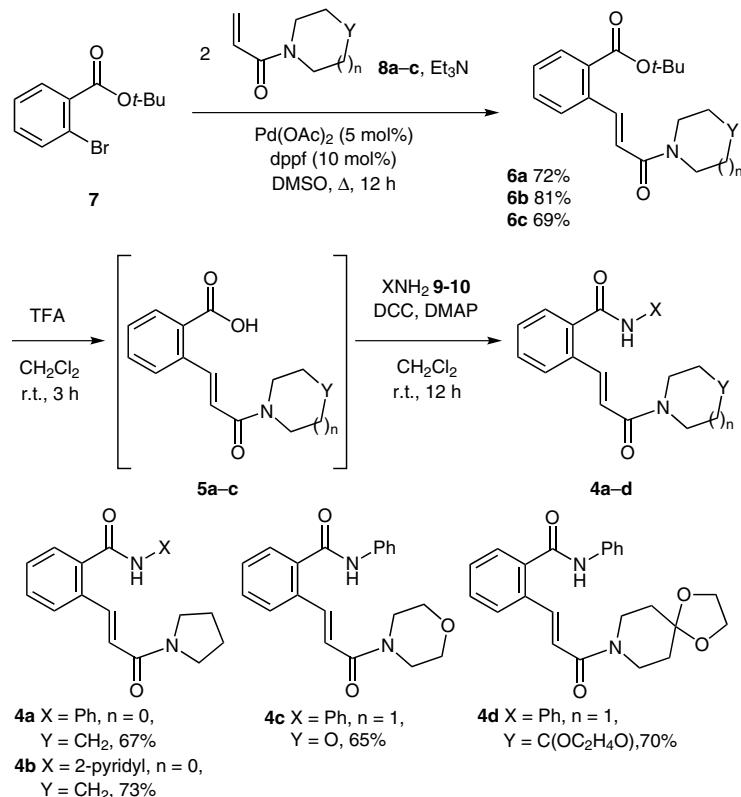
rated *tert*-butyl benzoic acid esters **6a–c**, which were readily prepared through a palladium-catalyzed Heck cross-coupling between aryl bromide **7** and various acrylamides **8a–c** (Scheme 2).

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-amino-pyridine **10** finally delivered the required parent amides **4a–d**. It was worth noting that this coupling reaction led

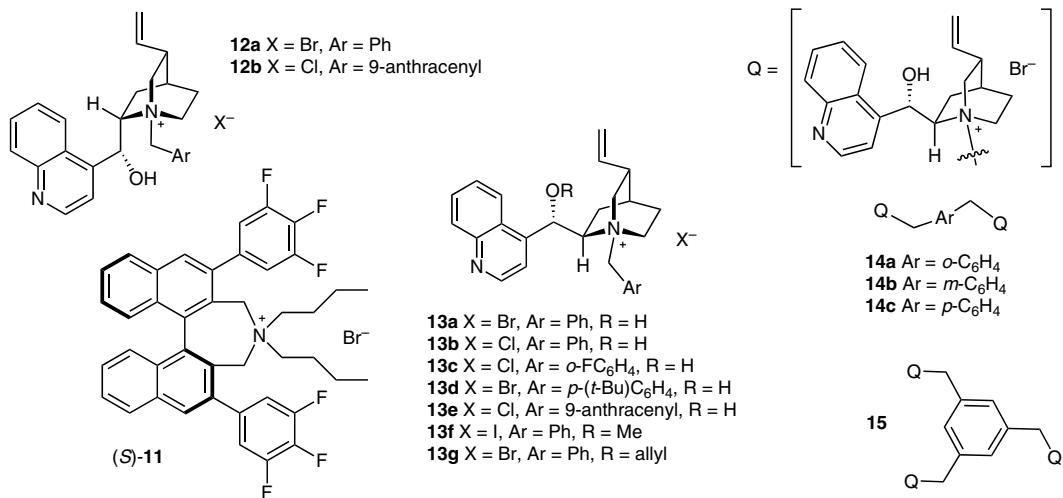
directly to the corresponding cyclized products **3** when acrylamide fragments were replaced by conjugated esters.

The asymmetric intramolecular aza-Michael reactions of substrates **4a–d** 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 Cs₂CO₃, 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 counterion 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).

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



Scheme 2 Synthesis of 3-substituted isoindolinone precursors

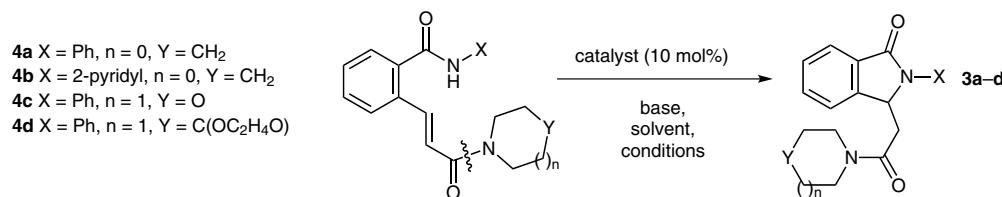


Scheme 3 Phase-transfer catalysts applied to the intramolecular aza-Michael reactions of reagents **4a–d**

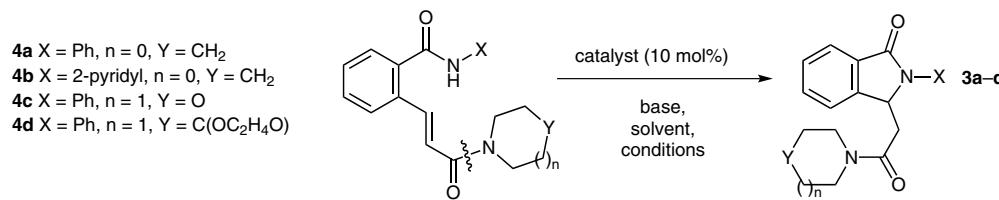
had no effect on the selectivity of the reaction (entry 16). The change from a benzyl to an anthracenyl group resulted in complete loss of enantioselection (entry 17). Disappointing results were also obtained from the functionalization of the alcohol fragment from cinchoninium **13a** (entries 18–20). Whereas an allyl function did not change the course of the reaction, provided Cs₂CO₃ 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 K₂CO₃ 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).

Table 1 Phase-Transfer-Catalyzed Intramolecular Aza-Michael Reaction of **4a–d**^a



Entry	Reagent	Catalyst	Base (1.3 equiv)	Solvent	Temp (°C)	Yield (%) ^b	ee (%) ^c
1	4a	none	Cs ₂ CO ₃	toluene	r.t.	74	0
2	4a	(<i>S</i>)- 11	Cs ₂ CO ₃	toluene	0	77	20
3	4a	12a	Cs ₂ CO ₃	toluene	r.t.	73	3
4	4a	12b	Cs ₂ CO ₃	toluene	r.t.	70	8
5 ^d	4a	13a	Cs ₂ CO ₃	toluene	r.t.	75	21
6	4a	13a	K ₃ PO ₄	toluene	r.t.	19	—
7	4a	13a	DBU	toluene	r.t.	78	6
8 ^e	4a	13a	KOH 50% aq.	toluene	r.t.	80	4
9	4a	13a	Cs ₂ CO ₃	THF	r.t.	76	7
10	4a	13a	Cs ₂ CO ₃	CH ₂ Cl ₂	r.t.	73	3

Table 1 Phase-Transfer-Catalyzed Intramolecular Aza-Michael Reaction of **4a–d^a** (continued)

Entry	Reagent	Catalyst	Base (1.3 equiv)	Solvent	Temp (°C)	Yield (%) ^b	ee (%) ^c
11	4a	13b	Cs ₂ CO ₃	toluene	r.t.	75	0
12 ^e	4a	13a	Cs ₂ CO ₃	toluene	r.t.	78	18
13 ^f	4a	13a	Cs ₂ CO ₃	toluene	r.t.	72	21
14	4a	13a	Cs ₂ CO ₃	toluene	0	75	0
15 ^{g,h}	4a	13c	Cs ₂ CO ₃	toluene	r.t.	74	0
16	4a	13d	Cs ₂ CO ₃	toluene	r.t.	77	20
17	4a	13e	Cs ₂ CO ₃	toluene	r.t.	73	0
18	4a	13f	Cs ₂ CO ₃	toluene	r.t.	80	0
19	4a	13g	Cs ₂ CO ₃	toluene	r.t.	74	21
20 ^g	4a	13g	KOH 50% aq.	toluene	r.t.	71	6
21	4a	14a	Cs ₂ CO ₃	toluene	r.t.	79	17
22	4a	14b	Cs ₂ CO ₃	toluene	r.t.	75	45
23	4a	14c	Cs ₂ CO ₃	toluene	r.t.	71	12
24	4a	15	Cs ₂ CO ₃	toluene	r.t.	78	76
25	4a	15	K ₂ CO ₃	toluene	r.t.	0	—
26	4a	15	Cs ₂ CO ₃	toluene	−5	69	45
27	4a	15	Cs ₂ CO ₃	CH ₂ Cl ₂	r.t.	73	2
28	4b	15	Cs ₂ CO ₃	toluene	r.t.	72	0
29	4c	15	Cs ₂ CO ₃	toluene	r.t.	80	59
30	4d	15	Cs ₂ CO ₃	toluene	r.t.	75	61

^a Reaction time: 24 h.^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% NaBF₄.^g The same result was obtained by using toluene-CHCl₃ (7:3).^h The same result was obtained by using KOH (50% aq) as base.

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.¹¹ 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.

Acknowledgment

The French ‘Ministère de la Recherche et des Nouvelles Technologies’ is gratefully acknowledged for a PhD fellowship (R.S.). Dr. F. Agbossou-Niedercorn and Dr. C. Michon thank the French National Research Agency for grant project ANR-09-BLAN-0032-02. Support from CNRS and Université Lille 1 is warmly acknowledged. Funding from the Région Nord-Pas de Calais with ‘Projet Prim: Etat-Région’ (mainly for SFC and elemental analysis equipment) and with ‘Fonds Européen de Développement Régional (FEDER)’ are also greatly appreciated. Ms C. Delabre (UCCS) is thanked for HPLC and GC-MS analyses. Ms M. Dubois (CMF) is thanked for

technical assistance and Dr. A. Couture for helpful comments. Dr. C. Michon dedicates this work to Prof. J. Lacour (University of Geneva).

Supporting Information for this article is available online at <http://www.thieme-connect.com/ejournals/toc/synlett>.

References

- (1) (a) Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1992**, *35*, 4613. (b) Pigeon, P.; Decroix, B. *Tetrahedron Lett.* **1996**, *37*, 7707. (c) Couture, A.; Deniau, E.; Grandclaudon, P. *Tetrahedron* **1997**, *53*, 10313. (d) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *J. Org. Chem.* **1998**, *63*, 3128. (e) Belliotti, T. R.; Brink, W. A.; Kesten, S. R.; Rubin, J. R.; Wustrow, D. J.; Zoski, K. T.; Whetzel, S. Z.; Corbin, A. E.; Pugsley, T. A.; Heffner, T. G.; Wise, L. D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1499. (f) Couture, A.; Deniau, E.; Grandclaudon, P.; Hoarau, C. *Tetrahedron* **2000**, *56*, 1491. (g) Riedlinger, C.; Endicott, J. A.; Kemp, S. J.; Smyth, L. A.; Watson, A.; Valeur, E.; Golding, B. T.; Griffin, R. J.; Hardeastle, I. R.; Noble, M. E.; McDonnel, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 16038.
- (2) (a) Uemura, S.; Fujita, T.; Sakaguchi, Y.; Kumamoto, E. *Biochem. Biophys. Res. Commun.* **2012**, *418*, 695. (b) Nishiyama, T.; Chiba, S.; Yamada, Y. *Eur. J. Pharmacol.* **2008**, *596*, 56. (c) Kanamitsu, N.; Osaki, T.; Itsuji, Y.; Yoshimura, M.; Tsujimoto, H.; Soga, M. *Chem. Pharm. Bull.* **2007**, *55*, 1682.
- (3) (a) Hussein, Z.; Mulford, D. J.; Bopp, B. A.; Granneman, G. R. *Br. J. Clin. Pharmacol.* **1993**, *36*, 357; *Chem. Abstr.* **1994**, *120*, 23014t. (b) Kondo, T.; Yoshida, K.; Yamamoto, M.; Tanayama, S. *Arzneim. Forsch.* **1996**, *46*, 11; *Chem. Abstr.* **1995**, *124*, 306386.
- (4) (a) Zhou, B.; Hou, W.; Yang, Y.; Li, Y. *Chem. Eur. J.* **2013**, *19*, 4701. (b) Zhu, C.; Falck, J. R. *Tetrahedron* **2012**, *68*, 9192. (c) Petronzi, C.; Collarile, S.; Croce, G.; Filosa, R.; De Caprariis, P.; Peduto, A.; Palombi, L.; Intintoli, V.; Di Mola, A.; Massa, A. *Eur. J. Org. Chem.* **2012**, 5357. (d) Zhu, C.; Falck, J. R. *Org. Lett.* **2011**, *13*, 1214. (e) Connolly, S.; Kristoffersson, A.; Skrinjar, M. PCT Int. Appl WO 2008099165, **2008**; *Chem. Abstr.* **2008**, *149*, 288691. (f) Dudash, J.; Rybczynski, P.; Urbanski, M.; Xiang, A.; Zeck, R.; Zhang, X.; Zhang, Y. U.S. Pat. Appl US 20070099930, **2007**; *Chem. Abstr.* **2007**, *146*, 481914. (g) Kanamitsu, N.; Osaki, T.; Itsuji, Y.; Yoshimura, M.; Tsujimoto, H.; Soga, M. *Chem. Pharm. Bull.* **2007**, *55*, 1682. (h) Grigg, R.; Gai, X.; Khamnaen, T.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. *Can. J. Chem.* **2005**, *83*, 990. (i) Gai, X.; Grigg, R.; Khamnaen, T.; Rajviroongit, S.; Sridharan, V.; Zhang, L.; Collard, S.; Keep, A. *Tetrahedron Lett.* **2003**, *44*, 7441. (j) Nageshwar Rao, I.; Prabhakaran, E. N.; Das, S. K.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 4079. (k) Bollbuck, B.; Eder, J.; Heng, R.; Revesz, L.; Schlapbach, A.; Waelchli, R. PCT Int. Appl WO 2004037796 A2, **2004**; *Chem. Abstr.* **2004**, *140*, 391295. (l) Love, C. J.; Leenaerts, J. E.; Cooymans, L. P.; Lebsack, A. D.; Branstetter, B. J.; Rech, J. C.; Gleason, E. A.; Venable, J. D.; Wiener, D.; Smith, D. M.; Breitenbucher, J. G. PCT Int. Appl WO 2009132000, **2009**; *Chem. Abstr.* **2009**, *151*, 508492.
- (5) Nishimura, M.; Sugawara, N.; Nigorikawa, Y.; Inomiya, N.; Ueda, K.; Ishii, A.; Kanemitsu, N. Jpn. Pat JP 2010241770, **2010**; *Chem. Abstr.* **2010**, *153*, 580344.
- (6) (a) Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633. (b) Vicario, J. L.; Badia, D.; Carrillo, L.; Etxebarria, J.; Reyes, E.; Ruiz, N. *Org. Prep. Proced. Int.* **2005**, *37*, 513. (c) Krishna, P. R.; Sreeshailam, A.; Srinivas, R. *Tetrahedron* **2009**, *65*, 9657. (d) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058. (e) Rulev, A. Y. *Russian Chem. Rev.* **2011**, *80*, 197. (f) Wang, J.; Li, P.; Choy, P. Y.; Chan, A. S. C.; Kwong, F. Y. *ChemCatChem* **2012**, *4*, 917.
- (7) (a) Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2013**, *52*, 4312. (b) Jew, S. S.; Park, H. G. *Chem. Commun.* **2009**, *7090*. (c) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (d) Ooi, T.; Maruoka, K. *Aldrichimica Acta* **2007**, *40*, 77. (e) Shirakawa, S.; Maruoka, K. In *Science of Synthesis, Asymmetric Organocatalysis*; Vol. 2; List, B.; Maruoka, K., Eds.; Thieme: Stuttgart, **2012**, 551. (f) Park, H.-G. In *Science of Synthesis, Asymmetric Organocatalysis*; Vol. 2; List, B.; Maruoka, K., Eds.; Thieme: Stuttgart, **2012**, 499.
- (8) (a) Aires-de-Sousa, J.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **1996**, *37*, 3183. (b) Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; Rosa, A. M.; Gomes, M. J. S.; Corvo, M. C.; Williams, D. J.; White, A. J. P. *Tetrahedron: Asymmetry* **2001**, *12*, 3349. (c) Fioravanti, R.; Mascia, M. G.; Pellacani, L.; Tardella, P. A. *Tetrahedron* **2004**, *60*, 8073. (d) Murugan, E.; Siva, A. *Synthesis* **2005**, 2022. (e) Minakata, S.; Murakami, Y.; Tsuruoka, R.; Kitanaka, S.; Komatsu, M. *Chem. Commun.* **2008**, 6363. (f) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 3238. (g) Tomooka, K.; Uehara, K.; Nishikawa, R.; Suzuki, M.; Igawa, K. *J. Am. Chem. Soc.* **2010**, *132*, 9232. (h) Mahé, O.; Dez, I.; Levacher, V.; Brière, J.-F. *Angew. Chem. Int. Ed.* **2010**, *49*, 7072. (i) Bandini, M.; Bottoni, A.; Eichholzer, A.; Miscione, G. P.; Stenta, M. *Chem. Eur. J.* **2010**, *16*, 12462. (j) Hu, J.; Liu, L.; Wang, X.; Hu, Y.; Yang, S.; Liang, Y. *Green Sustainable Chem.* **2011**, *1*, 165. (k) Wang, L.; Shirakawa, S.; Maruoka, K. *Angew. Chem. Int. Ed.* **2011**, *50*, 5327. (l) Mahé, O.; Dez, I.; Levacher, V.; Brière, J.-F. *Org. Biomol. Chem.* **2012**, *10*, 3946.
- (9) (a) Jung, M. E. In *Comprehensive Organic Synthesis*; Vol. 4; Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds.; Pergamon Press: Oxford, **1991**, 30; and references therein. (b) De, K.; Legros, L.; Crousse, B.; Bonnet-Delpont, D. J. *Org. Chem.* **2009**, *74*, 6260. (c) Wang, J.; Li, P.-F.; Chan, S. H.; Chan, A. S. C.; Kwong, F. Y. *Tetrahedron Lett.* **2012**, *53*, 2887. (d) Amara, Z.; Drège, E.; Trouflard, C.; Retailleau, P.; Joseph, D. *Org. Biomol. Chem.* **2012**, *10*, 7148. (e) Medina, F.; Michon, C.; Agbossou-Niedercorn, F. *Eur. J. Org. Chem.* **2012**, 6218. (f) Medina, F.; Duhal, N.; Michon, C.; Agbossou-Niedercorn, F. *C. R. Chim.* **2013**, *16*, 311.
- (10) (a) Jew, S. S.; Jeong, B. S.; Yoo, M. S.; Huh, H.; Park, H. G. *Chem. Commun.* **2001**, 1244. (b) Park, H. G.; Jeong, B. S.; Yoo, M. S.; Park, M. K.; Huh, H.; Jew, S. S. *Tetrahedron Lett.* **2001**, *42*, 4645. (c) Park, H. G.; Jeong, B. S.; Yoo, M. S.; Lee, J. H.; Park, M. K.; Lee, Y. J.; Kim, M. J.; Jew, S. S. *Angew. Chem. Int. Ed.* **2002**, *41*, 3036. (d) Jew, S. S.; Yoo, M. S.; Jeong, B. S.; Park, I. Y.; Park, H. G. *Org. Lett.* **2002**, *4*, 4245. (e) Kim, S.; Lee, J.; Lee, T.; Park, H. G.; Kim, D. *Org. Lett.* **2003**, *5*, 2703. (f) Danner, P.; Bauer, M.; Phukan, P.; Maier, M. E. *Eur. J. Org. Chem.* **2005**, 317. (g) Lee, J. H.; Jeong, B. S.; Ku, J. M.; Jew, S. S.; Park, H. G. *J. Org. Chem.* **2006**, *71*, 6690. (h) Lee, J. H.; Yoo, M. S.; Jung, J. H.; Jew, S. S.; Park, H. G.; Jeong, B. S. *Tetrahedron* **2007**, *63*, 7906. (i) Andrus, M. B.; Christiansen, M. A.; Hicken, E. J.; Gainer, M. J.; Bedke, D. K.; Harper, K. C.; Mikkelsen, S. R.; Dodson, D. S.; Harris, D. T. *Org. Lett.* **2007**, *9*, 4865. (j) Christiansen, M. A.; Butler, A. W.; Hill, A. R.; Andrus,

- M. B. *Synlett* **2009**, 653. (k) Ku, J.-M.; Jeong, B. S.; Jew, S. S.; Park, H. G. *J. Org. Chem.* **2007**, 72, 8115. (l) Li, M.; Zhou, P.; Roth, H. F. *Synthesis* **2007**, 55.
- (11) **General Procedure:** Benzamide **4a** (0.078 mmol), base (1.3 equiv) and catalyst (10 mol%) were stirred for 20 h at r.t. in toluene (1 mL). The resulting reaction was monitored by TLC until completion. The crude product was purified by flash chromatography on silica gel (EtOAc–hexane, 40:60) to afford, after evaporation of solvents, product **3a** as a white solid. The enantiomeric excess of **3a** was determined by HPLC analysis (Daicel Chiralpak AD CSP; hexane–EtOH (7:3); 20 °C; 0.5 mL/min; 275 nm).
- Compound 3a:** Mp 185 °C; R_f = 0.40 (EtOAc–hexane, 40:60); $[\alpha]_D^{20}$ +76 (*c* 0.43, CHCl₃, for 76% ee). IR: 1689, 1627, 1446, 1388, 1149, 758, 698 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.74–1.83 (m, 4 H, 2 × CH₂), 2.40 (dd, J = 15.6, 8.8 Hz, 1 H, CH₂CO), 2.85 (dd, J = 15.6, 4.3 Hz, 1 H, CH₂CO), 3.07–3.19 (m, 2 H, NCH₂), 3.34–3.55 (m, 2 H, NCH₂), 5.88 (dd, J = 8.8, 4.3 Hz, 1 H, NCH), 7.23 (t, J = 7.3 Hz, 1 H, Ar-H), 7.42–7.63 (m, 4 H, Ar-H), 7.63–7.68 (m, 3 H, Ar-H), 7.92 (d, J = 7.1 Hz, 1 H, Ar-H). ¹³C NMR (75

MHz, CDCl₃): δ = 168.1 (CO), 166.9 (CO), 145.3 (C), 136.7 (C), 132.3 (CH), 131.7 (C), 129.1 (2 × CH), 128.7 (CH), 125.5 (CH), 124.1 (CH), 123.3 (2 × CH), 123.2 (CH), 57.8 (CH), 46.6 (CH₂), 45.8 (CH₂), 38.5 (CH₂), 25.9 (CH₂), 24.3 (CH₂). Anal. Calcd for C₂₀H₂₀N₂O₂: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.20; H, 6.41; N, 8.64.

Compound 4a: Obtained from **6a** (2 mmol). Yield: 429 mg (67%); mp 194 °C; R_f = 0.62 (EtOAc). IR: 2970, 1672, 1647, 1585, 1442, 1327, 754, 690 cm⁻¹. ¹H NMR (300 MHz, CDCl₃): δ = 1.78–1.94 (m, 4 H, 2 × CH₂), 3.36–3.42 (m, 4 H, 2 × NCH₂), 6.53 (d, J = 15.6 Hz, 1 H, =CH), 7.11 (t, J = 7.4 Hz, 1 H, Ar-H), 7.28–7.43 (m, 5 H, Ar-H), 7.53 (d, J = 6.9 Hz, 1 H, Ar-H), 7.65–7.71 (m, 2 H, Ar-H), 7.76 (d, J = 15.6 Hz, 1 H, CH=), 8.67 (br s, 1 H, NH). ¹³C NMR (75 MHz, CDCl₃): δ = 167.6 (CO), 164.4 (CO), 138.8 (CH), 138.3 (C), 137.1 (C), 133.2 (C), 129.9 (CH), 129.0 (2 × CH), 128.0 (CH), 124.5 (CH), 122.1 (2 × CH), 120.1 (CH), 46.6 (CH₂), 46.0 (CH₂), 26.0 (CH₂), 24.1 (CH₂). Anal. Calcd for C₂₀H₂₀N₂O₂: C, 74.98; H, 6.29; N, 8.74. Found: C, 75.05; H, 6.20; N, 8.83.

Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.