Tetrahedron Letters xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Bifunctional cinchona alkaloid-squaramide-catalyzed highly enantioselective aza-Michael addition of indolines to α,β-unsaturated ketones

Arun K. Ghosh *, Bing Zhou

Department of Chemistry and Medicinal Chemistry, Purdue University, 560 Oval Drive, West Lafayette, IN 47907, United States

ARTICLE INFO

Article history:
Received 2 April 2013
Revised 16 April 2013
Accepted 19 April 2013
Available online xxxx

Keywords:
Aza-Michael reaction
Organocatalysis
Indoline
β-Keto indoline
Cinchona alkaloid
Enantioselective

ABSTRACT

An enantioselective aza-Michael addition of indolines to α,β-unsaturated ketones was achieved using a bifunctional cinchona alkaloid-derived chiral squaramide derivative. Various β-indolinyl ketone derivatives were obtained in good to excellent yields and with high enantioselectivity. DDQ or MnO_2 oxidation of indoline derivatives provided convenient access to various enantioenriched *N*-substituted indole derivatives.

The indole nucleus is a common structural feature in many bioactive alkaloids.[1] These subunits are also widely utilized in medicinal chemistry. Thus, enantioselective functionalization of indole ring is important. Over the years, a number of methods were developed which involved enantioselective alkylation of indoles at the C-3 position.[2] Recently, enantioselective alkylation of indoles at the C-2 has been carried out through the Pictet–Spengler reaction or alkylation/oxidation of 4,7-dihydroindoles.[3] However, enantioselective derivatization of indoles utilizing indole nitrogen atom has rarely been explored possibly due to its low nucleophilicity.[4] Interestingly, such *N*-functionalized indole derivatives are important structural elements of numerous biologically active natural products and synthetic medicinal agents.[5,6]

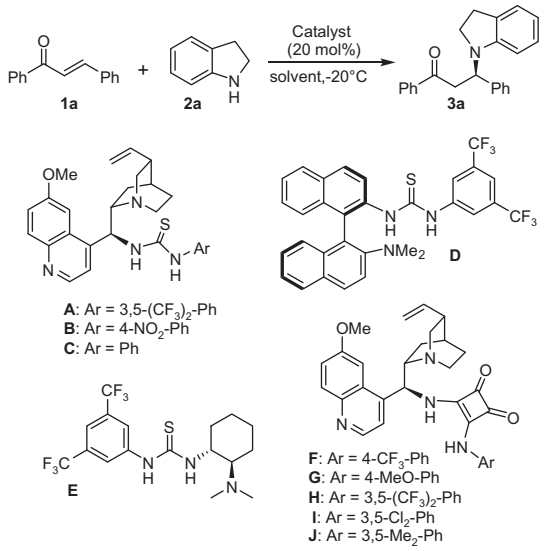
Asymmetric Michael addition of nitrogen to α,β-unsaturated carbonyl derivatives represents a straightforward, logical approach. A number of methods have been developed relying upon the use of chiral auxiliaries, chiral starting materials, or stoichiometric amounts of chiral ligands. However, the catalytic enantioselective aza-Michael addition to α,β-unsaturated carbonyl compounds is quite challenging and remained relatively unexplored until recently.[7] In 2006, MacMillian and co-workers[8] reported an enantioselective secondary amine-catalyzed intermolecular aza-Michael addition of *N*-silyloxycarbamates to α,β-unsaturated aldehydes. Subsequently, several other conjugate additions catalyzed by secondary amines were investigated.[9] The scope of these protocols was extended to α,β-unsaturated aliphatic ketones using primary amines and α,β-unsaturated aromatic ketones using chiral phosphoric acids as the catalyst.[10,11] Recently, bifunctional urea derived catalysts were employed for aza-Michael addition, however low enantioselectivity of products and high catalyst loading were some of the drawbacks of these methodologies.[12] Enantioselective aza-Michael addition of indole or indoline has been limited. Recent report of enantioselective aza-Michael addition of indoline to β-nitro styrene only provided 28% ee.[13] Herein, we describe an enantioselective intermolecular aza-Michael reaction of indolines with α,β-unsaturated aromatic ketones catalyzed by a bifunctional cinchona alkaloid-squaramide catalyst. The resulting indoline derivative can be converted into indole derivative by a mild oxidation protocol. The current methodology provides access to a range of enantioenriched *N*-substituted indoles with good to excellent enantioselectivity.

Our studies were focused on the aza-Michael reaction between chalcone **1a** and indoline **2a** catalyzed by various quinine thiourea derivatives. Initially, we performed all reactions with 20 mol % catalyst in toluene at −20 °C. The results are shown in Table 1. As can be seen, when thiourea catalyst **A**[14] was used, the addition product **3a** showed moderate enantioselectivity (55% *ee*) and the conversion was excellent (90%, entry 1). We examined various other thiourea catalysts **B**–**E**.[15] However, these catalysts showed moderate enantioselectivity for the product **3a** (entries 2–5). Subsequently, we investigated squaramide derivatives of quinine **F**–**J** (entries

* Corresponding author. Tel.: +1 765 494 5323.
E-mail address: akghosh@purdue.edu (A.K. Ghosh).

0040-4039/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2013.04.080

Table 1
Screening of the reaction conditions[a]



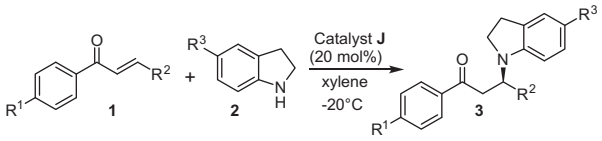
Entry	Catalyst	Solvent	Conv[b] (%)	*ee*[c] (%)
1	**A**	PhMe	90	55
2	**B**	PhMe	70	52
3	**C**	PhMe	34	45
4	**D**	PhMe	20	25
5	**E**	PhMe	82	50
6	**F**	PhMe	56	60
7	**G**	PhMe	20	40
8	**H**	PhMe	88	69
9	**I**	PhMe	25	70
10	**J**	PhMe	76	78
11	**J**	CH_2Cl_2	94	70
12	**J**	Et_2O	60	76
13	**J**	CH_3CN	50	45
14	**J**	Xylene	83	81
15[d]	**J**	Xylene	92	72
16[e]	**J**	Xylene	60	80

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1a**, 0.2 mmol of **2a**, and 20 mol % of catalysts in 1 mL solvent at −20 °C for 7 days.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by HPLC analysis.
[d] Reaction was conducted at −10 °C.
[e] Reaction was conducted at −30 °C.

6–10).[16] Interestingly, squaramide catalyst **J** showed much improvement in enantioselectivity (78% *ee*, entry 10), however, conversion (76%) was less satisfactory. In an effort to improve conversion, we examined various solvents for catalyst **J** (entries 10–14). As it turned out, nonpolar solvents were more suitable for optimal conversion and product enantioselectivity. Aza-Michael reaction of **1a** and **2a** catalyzed by squaramide derivative **J** (20 mol %) provided the best result with 83% conversion and 81% *ee* for the addition product **3a** (entry 14). Raising the reaction temperature to −10 °C resulted in improvement of conversion (92%) however, enantioselectivity was reduced to 72% *ee* (entry 15). Also, lowering of reaction temperature to −30 °C did not improve enantioselectivity and a relatively low conversion (60%) was observed (entry 16). From the above studies, we concluded that squaramide catalyst **J** (20 mol %) in xylene at −20 °C would be the optimum condition for best enantioinduction and conversion.

We then explored aza-Michael reactions with a variety of α,β-unsaturated ketones **1** and indolines **2** using catalyst **J** in xylene at −20 °C. The results are shown in Table 2. First, we examined various electron-donating and electron-withdrawing substituents on the phenyl and benzoyl rings (**1a**–**i**).[17] As can be seen, substituents

Table 2
Asymmetric aza-Michael reaction of indolines and α,β-unsaturated ketones[a]



Entry	R^1, R^2, R^3	Product	Yield[b] (%)	*ee*[c] (%)
1	H, Ph, H	**3a**	74 (89)	81
2	CH_3, Ph, H	**3b**	54 (85)	84
3	Br, Ph, H	**3c**	60 (88)	83
4	H, 4-CH_3-Ph, H	**3d**	55 (83)	86
5	H, 4-CF_3-Ph, H	**3e**	84	95
6	H, 4-Br-Ph, H	**3f**	86	96
7	H, 4-Cl-Ph, H	**3g**	83	92
8	H, 3-Cl-Ph, H	**3h**	84	90
9	H, 4-CN-Ph, H	**3i**	40 (87)	90
10	H, 2-furyl, H	**3j**	55 (84)	80
11	H, Me, H	**3k**	57	84
12	H, 4-Br-Ph, Br	**3l**	54 (84)	80
13	H, 4-CF_3-Ph, Cl	**3m**	53 (90)	80
14	H, 4-CF_3-Ph, Me	**3n**	93	99
15	H, 4-CF_3-Ph, MeO	**3o**	94	95
16	H, 4-Br-Ph, Me	**3p**	94	99

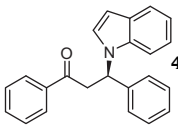
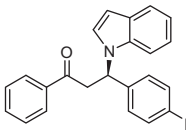
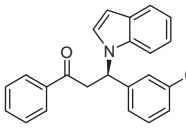
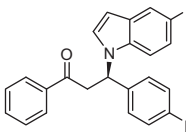
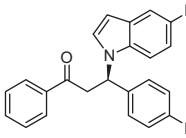
[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **1**, 0.2 mmol of **2**, and 20 mol % of catalyst **J** in 1 mL xylene at −20 °C for 7 days.
[b] Yield of isolated product. Yields in parentheses are based upon recovered starting material.
[c] Determined by HPLC analysis.

on the benzoyl ring (R^1) have little effect on the enantioselectivity and isolated yields were moderate because of significantly low conversion (entries 2 and 3). Incorporation of an electron-donating group on the phenyl ring (R^2) did not improve conversion (entry 4). Electron-withdrawing substituents on the phenyl ring resulted in both improvement in enantioselectivity and yield of addition products (entries 5–8). Interestingly, *p*-nitrile group on the phenyl ring provided low isolated yield of the product possibly due to hydrogen bonding interaction of a CN-group with the squaramide catalyst (entry 9). Significantly, furyl and methyl β-substituted α,β-unsaturated ketones were also shown to be compatible with the reaction conditions. The corresponding products **3j** and **3k** were isolated in moderate yields but with good enantioselectivity (entries 10 and 11). We have explored substituted indolines containing either an electron-withdrawing group or electron-donating group (5-Br, 5-Cl, 5-Me, and 5-OMe, respectively), for these aza-Michael reactions (entries 12–16). Indolines with electron-donating groups were much more reactive toward conjugate addition and gave Michael adducts in higher yields, and with higher enantioselectivity (entries 14–16). The absolute configuration of products was determined to be *R* as depicted based upon stereochemical outcome of previous 1,4-addition reactions catalyzed by quinine-derived squaramide catalysts.[16b,18]

We have converted a number of aza-Michael indoline products into the corresponding *N*-substituted indole derivatives by mild oxidation.[13b] As shown in Table 3, oxidation of various Michael adducts with DDQ (1.05 equiv) in THF at 23 °C for 15 min afforded the *N*-substituted indole derivatives in excellent yields without loss of enantioselectivity (entries 1–4). Similarly, oxidation of Michael adducts with MnO_2 (10 equiv) in CH_2Cl_2 also provided enantioenriched *N*-substituted indole derivatives in excellent yields without any loss of optical purity (entry 5).

In summary, we have developed an enantioselective protocol for aza-Michael additions of indolines to α,β-unsaturated ketones by utilizing bifunctional cinchona alkaloid–squaramide derivatives as catalysts. This asymmetric reaction provided excellent yields and good to excellent enantioselectivity for a variety of substituted

Table 3
Synthesis of *N*-substituted indoles[a]

Entry	Indoline	Product	Yield[b] (%)	*ee*[c] (%)
1	**3a**	 **4a**	92	80
2	**3f**	 **4f**	93	94
3	**3h**	 **4h**	95	92
4	**3l**	 **4l**	93	80
5[d]	**3p**	 **4p**	94	99

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **3** and 0.105 mmol of DDQ in 1 mL THF at 23 °C for 15 min.
[b] Yield of isolated product.
[c] Determined by HPLC analysis.
[d] Using MnO_2 (10 equiv) as oxidizing agent.

chalcones. The indoline derivatives can be oxidized to indoles conveniently without loss of enantioselectivity. The present aza-Michael reaction provides access to highly enantiopure *N*-substituted indole and indoline derivatives. Further applications of this methodology are in progress in our laboratories.

Acknowledgments

Financial support of this work was provided by the National Institutes of Health and Purdue University. We thank Mr. Siddhartha Akasapu (Purdue University) for helpful discussions.

References and notes

1. (a) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; (b) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875; (c) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843; (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.
2. (a) Bandini, M.; Melloni, A.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 550; (b) Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199; (c) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190; (d) Terrasson, V.; Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635.
3. (a) Kang, Q.; Zheng, X.-J.; You, S.-L. *Chem. Eur. J.* **2008**, *14*, 3539; (b) Zeng, M.; Kang, Q.; He, Q.-L.; You, S.-L. *Adv. Synth. Catal.* **2008**, *350*, 2169; (c) Sheng, Y.-F.; Li, G.-Q.; Kang, Q.; Zhang, A.-J.; You, S.-L. *Chem. Eur. J.* **2009**, *15*, 3351; (d) Hong, L.; Liu, C.; Sun, W.; Wang, L.; Wong, K.; Wang, R. *Org. Lett.* **2009**, *11*, 2177; (e) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wong, K.; Wang, R. *Chem. Eur. J.* **2009**, *15*, 11105; (f) Schipper, D. J.; Hutchinson, M.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6910. and references cited therein.
4. (a) Trost, B. M.; Krische, M. J.; Berl, V.; Grenzer, E. M. *Org. Lett.* **2002**, *4*, 2005; (b) Bandini, M.; Eichholzer, A.; Tragni, M.; Umani-Ronchi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 3238; (c) Cui, H.-L.; Feng, X.; Peng, J.; Lei, J.; Jiang, K.; Chen, Y.-C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5737; (d) Enders, D.; Wang, C.; Raabe, G. *Synthesis* **2009**, *5*, 4119; (e) Hong, L.; Sun, W.; Liu, C.; Wang, L.; Wang, R. *Chem. Eur. J.* **2010**, *16*, 440; (f) Trost, B. M.; Osipov, M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 15800; (g) Cai, Q.; Zheng, C.; You, S.-L. *Angew. Chem., Int. Ed.* **2010**, *49*, 8666; (h) Stanley, L. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2009**, *48*, 7841; (i) Liu, W.-B.; Zhang, X.; Dai, L.-X.; You, S.-L. *Angew. Chem., Int. Ed.* **2012**, *51*, 5183.
5. (a) Tillequin, F.; Koch, M.; Bert, M.; Sevenet, T. *J. Nat. Prod.* **1979**, *42*, 92; (b) Orlemans, E. O. M.; Verboom, W.; Scheltinga, M. W.; Reinhoudt, D. N.; Lelieveld, P.; Fiebig, H. H.; Winterhalter, B. R.; Double, J. A.; Bibby, M. C. *J. Med. Chem.* **1989**, *32*, 1612; (c) Paris, D.; Cottin, M.; Demonchaux, P.; Augert, G.; Dupassieux, P.; Lenoir, P.; Peck, M. J.; Jasserand, D. *J. Med. Chem.* **1995**, *38*, 669; (d) Mahaney, P. E.; Vu, A. T.; McComas, C. C.; Zhang, P.; Nogle, L. M.; Watts, W. L.; Sarkahian, A.; Leventhal, L.; Sullivan, N. R.; Uveges, A. J.; Trybulski, E. J. *Bioorg. Med. Chem.* **2006**, *14*, 8455; (e) Fernandez, L. S.; Buchanan, M. S.; Carroll, A. R.; Feng, Y. J.; Quinn, R. J.; Avery, V. M. *Org. Lett.* **2009**, *11*, 329.
6. Cardillo, G.; Tomasini, C. *Chem. Soc. Rev.* **1996**, *25*, 117.
7. For recent reviews on asymmetric aza-Michael reactions, see: (a) Wang, J.; Li, P.; Choy, P. Y.; Chan, A. S. C.; Kwong, F. Y. *ChemCatChem* **2012**, *4*, 917; (b) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058.
8. Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328.
9. (a) Diner, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1983; (b) Lin, Q.-Y.; Meloni, D.; Pan, Y.-C.; Xia, M.; Rodgers, J.; Shepard, S.; Li, M.; Galya, L.; Metcalf, B.; Yue, T.-Y.; Liu, P.-L.; Zhou, J. *Org. Lett.* **2009**, *11*, 1999; (c) Fustero, S.; Moscardo, J.; Jimenez, D.; Perez-Carrion, M. D.; Sanchez-Rosello, M.; del Pozo, C. *Chem. Eur. J.* **2008**, *14*, 9868; (d) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Cordova, A. *Angew. Chem. Int. Ed.* **2007**, *46*, 778; (e) Li, H.; Zu, L.-S.; Xie, H. X.; Wang, J.; Wang, W. *Chem. Commun.* **2008**, 5636; (f) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Cordova, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8468; (g) Uria, U.; Reyes, E.; Vicario, J. L.; Badia, D.; Carrillo, L. *Org. Lett.* **2011**, *13*, 336; (h) Guo, H.-M.; Yuan, T.-F.; Niu, H.-Y.; Liu, J.-Y.; Mao, R.-Z.; Li, D.-Y.; Qu, G.-R. *Chem. Eur. J.* **2011**, *17*, 4095; (i) Li, H.; Zhao, J.; Zeng, L.; Hu, W. *J. Org. Chem.* **2011**, *76*, 8064.
10. (a) Lu, X.; Deng, L. *Angew. Chem. Int. Ed.* **2008**, *47*, 7710; (b) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem. Int. Ed.* **2008**, *47*, 8703; (c) Luo, G.; Zhang, S.; Duan, W.; Wang, W. *Synthesis* **2009**, 1564; (d) Gogoi, S.; Zhao, C.-G.; Ding, D. *Org. Lett.* **2009**, *11*, 2249; (e) Lv, J.; Wu, H.; Wang, Y. *Eur. J. Org. Chem.* **2010**, 2073; (f) Liu, J.-D.; Chen, Y.-C.; Zhang, G.-B.; Li, Z.-Q.; Chen, P.; Du, J.-Y.; Tu, Y.-Q.; Fan, C.-A. *Adv. Synth. Catal.* **2011**, *353*, 2721.
11. (a) Enders, D.; Narine, A.; Toulgoat, F.; Bisschops, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 5661; (b) Yang, L.; Xia, C.; Huang, H. *Chin. J. Catal.* **2011**, *32*, 1573; (c) Feng, Z.; Xu, Q.-L.; Dai, L.-X.; You, S. L. *Heterocycles* **2010**, *80*, 765.
12. (a) Wang, J.; Zu, L.; Li, H.; Xie, H.; Wang, W. *Synthesis* **2007**, 2576; (b) Pettersen, D.; Piana, F.; Bernardi, L.; Fini, F.; Fochi, M.; Sgarzani, V.; Ricci, A. *Tetrahedron Lett.* **2007**, *48*, 7805; (c) Sibi, M. P.; Itoh, K. *J. Am. Chem. Soc.* **2007**, *129*, 8064; (d) Lykke, L.; Monge, D.; Nielsen, M.; Jorgensen, K. A. *Chem. Eur. J.* **2010**, *16*, 13330; (e) Gu, Q.; You, S. L. *Chem. Sci.* **2011**, *2*, 1519.
13. (a) Kilic, H.; Bayindir, S.; Erdogan, E.; Saracoglu, N. *Tetrahedron* **2012**, *68*, 5619; (b) Bayindir, S.; Erdogan, E.; Kilic, H.; Saracoglu, N. *Synlett* **2010**, 1455.
14. Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.
15. (a) Song, J.; Wang, Y.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 6048; (b) Galzerano, P.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Giannichi, B.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2009**, *15*, 7846; (c) Okino, T.; Hoashi, Y.; Takemoto, T. *J. Am. Chem. Soc.* **2003**, *125*, 12672; (d) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 119.
16. (a) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416; (b) Yang, W.; Du, D.-M. *Org. Lett.* **2010**, *12*, 5450.
17. For details, please see supplementary data.
18. Selected examples of squaramide catalyzed 1,4-additions: (a) Dai, L.; Wang, S.-X.; Chen, F.-E. *Adv. Synth. Catal.* **2010**, *352*, 2137; (b) Yang, W.; Du, D.-M. *Chem. Commun.* **2011**, *47*, 12706; (c) Yang, W.; Du, D.-M. *Org. Biomol. Chem.* **2012**, *10*, 6876; (d) Ling, J.-B.; Su, Y.; Zhu, H.-L.; Wang, G. Y.; Xu, P. F. *Org. Lett.* **2012**, *14*, 1090; (e) Kasaplar, P.; Riente, P.; Hartmann, C.; Pericas, M. A. *Adv. Synth. Catal.* **2012**, *354*, 2905.