ORGANIC LETTERS

2013
Vol. 15, No. 8
1874–1877

An Expedient Route to Imidazo[1,4]diazepin-7-ones via A Post-Ugi Gold-Catalyzed Heteroannulation

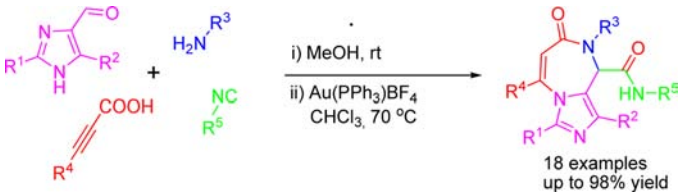
Amit Kumar,[†] Zhenghua Li,[†] Sunil K. Sharma,[‡] Virinder S. Parmar,[‡] and Erik V. Van der Eycken*,[†]

Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, B-3001 Leuven, Belgium, and Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi-110 007, India

erik.vandereycken@chem.kuleuven.be

Received February 25, 2013

ABSTRACT



A novel diversity-oriented post-Ugi/gold(I)-catalyzed heteroannulation process for the synthesis of imidazo[1,4]diazepin-7-ones is elaborated. The scope and limitations of the protocol are discussed.

Homogeneous gold-catalyzed carbocyclization and heteroannulation strategies have become a particularly active research area due to the exceptional ability of gold complexes to activate alkynes, alkenes, and allenes toward nucleophilic attack.[1] The rediscovering of this coinage metal in homogeneous catalysis allowed a significant expansion of the current synthetic scenario for selective manipulations of unactivated unsaturated hydrocarbons. The gold-catalyzed intramolecular cyclizations of aromatic and heteroaromatic compounds with alkynes offer new pathways for the efficient construction of bioactive compounds.[2,3]

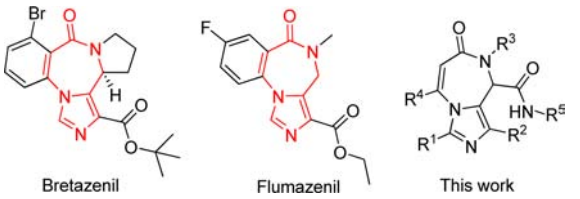


Figure 1. Drugs possessing the imidazo[1,4]diazepin-7-one skeleton.

[†] University of Leuven (KU Leuven).
[‡] University of Delhi.

(1) For selected reviews, see: (a) Fürstner, A.; Davies, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Li, Z.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (e) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (f) Hashmi, A. S. K.; Rudolph, M. *Chem. Soc. Rev.* **2008**, *37*, 1766. (g) Shen, H. C. *Tetrahedron* **2008**, *64*, 3885. (h) Shen, H. C. *Tetrahedron* **2008**, *64*, 7847. (i) Muzart, J. *Tetrahedron* **2008**, *64*, 5815. (j) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208.

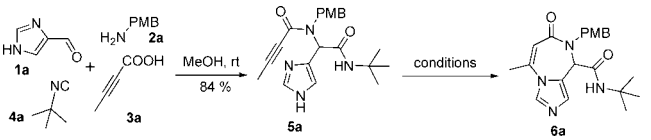
(2) (a) Rudolph, M.; Hashmi, A. S. K. *Chem. Commun.* **2011**, *47*, 6536. (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448. (c) Jiménez-Núñez, E.; Echavarren, A. M. *Chem. Commun.* **2007**, 333. (d) Echavarren, A. M. *Nat. Chem.* **2009**, *1*, 431. (e) Hashmi, A. S. K.; Yang, W.; ominger, F. *Angew. Chem., Int. Ed.* **2011**, *50*, 5762. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266. (g) Bandini, M. *Chem. Soc. Rev.* **2011**, *40*, 1358. (h) Bandini, M.; Bottoni, A.; Chiarucci, M.; Cera, G.; Miscione, G. P. *J. Am. Chem. Soc.* **2012**, *134*, 20690.

(3) (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 1105. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem.—Eur. J.* **2007**, *13*, 1358. (c) Vachhani, D. D.; Modha, S. G.; Sharma, A.; Van der Eycken, E. V. *Tetrahedron* **2013**, *69*, 359. (d) Vachhani, D. D.; Mehta, V. P.; Modha, S. G.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Adv. Synth. Catal.* **2012**, *354*, 1593.

10.1021/ol400526a
Published on Web 04/01/2013

The imidazodiazepinone core is ubiquitous in various natural and synthetic pharmaceuticals[4] as well as vital intermediates in the synthesis of pentostanin[5] and coformycin,[6] both naturally occurring anticancer and antiviral nucleosides. The commercially available drug bretazenil[7] is used as a partial agonist for $GABA_A$ receptors due to its high affinity to the benzodiazepinone binding site. On the other hand, flumazenil[8] is a high-affinity $GABA_A$-B_Z site antagonist that has been used clinically to treat benzodiazepine intoxication[9] (Figure 1). Most synthetic approaches toward imidazo[1,4]diazepinones involve multiple-step sequences and harsh conditions and are limited in scope of the substitution pattern of the scaffold.[10] Consequently, it would be highly desirable to develop a more versatile and milder route for these compounds. Through the years, multicomponent reactions (MCRs)[11] have received increasing attention due to their simplicity, efficiency, atom economy, shortend reaction times, and the possibilty for diversity-oriented synthesis. The combination of MCRs with transition metal-catalysis gives access to complex molecules in few steps as compared to traditional multistep processes. We have recently developed a sequential post-Ugi gold(I)-catalyzed intramolecular hydroarylation approach for the synthesis of indolazocines,[12] spiroindolines,[13] pyrroloazepinones, and pyrrolopyridinones.[14] Inspired by these findings and as a result of our interest in exploring the synthetic utility of both transition metal catalysis[15] and multicomponent reactions,[16] we have developed an expedient post-Ugi intramolecular

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst (mol %)	solvent	time (h)	conversion[b] (%) (yield %)
1	AuCl (10)	$CDCl_3$	24	100 (80)
2	$AuCl_3$(10)	$CDCl_3$	24	100 (72)
3	$Au(PPh_3)Cl$ (10)	$CDCl_3$	24	20
4	$Au(PPh_3)OTf$ (10)	$CDCl_3$	10	100 (96)
5	$Au(PPh_3)SbF_6$(10)	$CDCl_3$	24	60
6[c]	$Au(PPh_3)BF_4$(10)	$CDCl_3$	24	65
7	**$Au(PPh_3)BF_4$(10)**	**$CDCl_3$**	**4**	**100 (98)**
8	$Au(PPh_3)NTf_2$(10)	$CDCl_3$	24	100 (96)
9	Au(X-PhOS)NTf_2(10)	$CDCl_3$	12	100(92)
10	[MeCN(JohnPhos)Au] SbF_6 (10)	$CDCl_3$	24	100 (90)
11	$AgBF_4$ (10)	$CDCl_3$	24	100(84)
12	Cu(I)OTf (10)	$CDCl_3$	24	0
13	Sc(III)$(OTf)_3$ (10)	$CDCl_3$	24	5
14	Bi(III)$(OTf)_3$ (10)	$CDCl_3$	24	25
15	$Au(PPh_3)BF_4$(10)	ACN-d_3	6	100 (86)
16	$Au(PPh_3)BF_4$(10)	THF-d_8	24	90
17	$Au(PPh_3)BF_4$(5)	$CDCl_3$	24	45
18		$CDCl_3$	24	traces

[a] All reactions were run on a 0.13 mmol scale of **5a** in a screw-capped vial at 70 °C. [b] Conversion based on ^1H NMR analysis; yields given in parentheses are isolated yields. [c] Reaction at 50 °C. Tf = Trifluoromethanesulfonyl, X-Phos = 2-dicyclohexylphosphino-2′4′6′-triisopropylbiphenyl, JohnPhos = (2-biphenyl)di-*tert*-butylphosphine, PMB = *p*-methoxybenzyl.

(4) (a) Showalter, H. D. H.; Putt, S. R.; Borondy, P. E.; Shillis, J. L. *J. Med. Chem.* **1983**, *26*, 1478. (b) Saville-Stones, E. A.; Turner, R. M.; Lindell, S. D.; Jennings, N. S.; Head, J. C.; Carver, D. S. *Tetrahedron* **1994**, *50*, 6695. (c) Kasibhatla, S. R.; Bookser, B. C.; Xiao, W.; Erion, M. D. *J. Med. Chem.* **2001**, *44*, 613. (d) Bookser, B. C.; Kasibhatla, S. R.; Erion, M. D. *J. Med. Chem.* **2000**, *43*, 1519. (e) Kasibhatla, S. R.; Bookser, B. C.; Probst, G.; Appleman, J. R.; Erion, M. D. *J. Med. Chem.* **2000**, *43*, 1508. (f) Kasibhatla, S. R.; Bookser, B. C.; Appleman, J. R.; Erion, M. D. *J. Med. Chem.* **2000**, *43*, 1495. (g) Erion, M. D.; Kasibhatla, S. R.; Bookser, B. C.; van Poejie, P. D.; Reddy, M. R.; Gruber, H. E.; Appleman, J. R. *J. Am. Chem. Soc.* **1999**, *121*, 308. (h) Kieć-Kononowicza, K.; Karolak-Wojciechowskab, J.; Müllerc, C. E.; Schumacher, B.; Pekalaa, E.; Szymańskaa, E. *Eur. J. Med. Chem.* **2001**, *36*, 407. (I) Chen, B-C; Chao, S. T; Sundeen, J. E.; Tellew, J.; Ahmad, S. *Tetrahedron Lett.* **2002**, *43*, 1595.

(5) Baker, D. C.; Putt, S. R. *J. Am. Chem. Soc.* **1979**, *101*, 6127. Showalter, H. D. H.; Putt, S. R. *Tetrahedron Lett.* **1981**, *22*, 3155. Chan, E.; Putt, S. R.; Showalter, H. D. H.; Baker, D. C. *J. Org. Chem.* **1982**, *47*, 3457.

(6) Hawkins, L. D.; Hanvey, J. C.; Boyd, F. L., Jr.; Baker, D. C. *Nucleosides Nucleotides* **1983**, *2*, 479.

(7) Tashma, Z.; Raveh, L.; Liani, H.; Alkalay, D.; Givoni, S.; Kapon, J.; Cohen, G.; Alcalay, M.; Grauer, E. *J. Appl. Toxicol.* **2001**, *21*, S115.

(8) (a) Lancel, M.; Steiger, A. *Angew. Chem., Int. Ed.* **1999**, *111*, 2852. (b) Moran, M. D.; Wilson, A. A.; Elmore, C. S.; Parkes, J.; Ng, A.; Sadovski, O.; Graff, A.; Daskalakis, Z. J.; Houle, S.; Chapdelaine, M. J.; Vasdev, N. *Bioorg. Med. Chem.* **2012**, *20*, 4482.

(9) Lheureux, P.; Askenasi, R. *Hum. Toxicol.* **1988**, *7*, 165.

(10) (a) Achermann, G.; Ballard, T. M.; Blasco, F.; Broutin, P.-E.; Buttelmann, B.; Fischer, H.; Graf, M.; Hernandez, M.-C.; Hilty, P.; Knoflach, F.; Koblet, A.; Knust, H.; Kurt, A.; Martin, J. R.; Masciadri, R.; Porter, R. H. P.; Stadler, H.; Thomas, A. W.; Trube, G.; Wichmann, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5746. (b) Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282. (c) Zhang, P.; Zhang, W.; Liu, R.; Harris, B.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1995**, *38*, 1679. (d) Li, X.; Cao, H.; Zhang, C.; Furtmueller, R.; Fuchs, K.; Huck, S.; Sieghart, W.; Deschamps, J.; Cook, J. M. *J. Med. Chem.* **2003**, *46*, 5567. (e) Li, X.; Yu, J.; Atack, J. R.; Cook, J. M. *Med. Chem. Res.* **2004**, *13*, 259. (f) Marcos, A.; Pedregal, C.; Avendailo, C. *Tetrahedron* **1991**, *41*, 1459. (g) Rogers-Evans, M.; Spurr, P.; Hennig, M. *Tetrahedron Lett.* **2003**, *44*, 2425. (h) Donohue, S. R.; Dannals, R. F. *Tetrahedron Lett.* **2009**, *50*, 7271.

(11) For isonitrile-based multicomponent reactions, see (a) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (b) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. For multicomponent reactions with indoles, see: (c) Shriri, M. *Chem. Rev.* **2012**, *112*, 3508. For asymmetric multicomponent reactions, see: (d) Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. For multicomponent reactions in general, see: (e) Ganem, B. *Acc. Chem. Res.* **2009**, *42*, 463. (f) ElKaïm, L.; Grimaud, L. *Mol. Diversity* **2010**, *14*, 855. (g) Ruijter, E.; Scheffelaar, R.; Orru, R. V. A. *Angew.Chem., Int. Ed.* **2011**, *50*, 6234. (h) Dömling, A.; Wang, W.; Wang, K. *Chem. Rev.* **2012**, *112*, 3083.

(12) Modha, S. G.; Vachhani, D. D.; Jacobs, J.; Van Meervelt, L.; Van der Eycken, E. V. *Chem. Commun.* **2012**, *48*, 6550.

(13) Modha, S. G.; Kumar, A.; Vachhani, D. D.; Jacobs, J.; Sharma, S. K.; Parmar, V. S.; Van Meervelt, L.; Van der Eycken, E. V. *Angew. Chem., Int. Ed.* **2012**, *51*, 9572.

(14) Modha, S. G.; Kumar, A.; Vachhani, D. D.; Jacobs, J.; Sharma, S. K.; Parmar, V. S.; Van Meervelt, L.; Van der Eycken, E. V. *Chem. Commun.* **2012**, *48*, 10916.

(15) (a) Modha, S. G.; Trivedi, J. C.; Mehta, V. P.; Ermolat'ev, D. S.; Van der Eycken, E. V. *J. Org. Chem.* **2011**, *76*, 846. (b) Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2011**, *40*, 4925. (c) Kappe, C. O.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2010**, *39*, 1280. (d) Donets, P. A.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Org. Lett.* **2009**, *11*, 3618. (e) Donets, P. A.; Van der Eycken, E. V. *Synthesis* **2011**, 2147. (f) Modha, S. G.; Mehta, V. P.; Ermolat'ev, D. S; Balzarini, J.; Van Hecke, K.; Van Meervelt, L.; Van der Eycken, E. V. *Mol. Diversity* **2010**, *14*, 767.

(16) (a) Mehta, V. P.; Modha, S. G.; Ruijter, E.; Van Hecke, K.; Van Meervelt, L.; Pannecouque, C.; Balzarini, J.; Orru, R. V. A.; Van der Eycken, E. V. *J. Org. Chem.* **2011**, *76*, 2828. (b) Peshkov, V. A.; Pereshivko, O. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2012**, *41*, 3790.

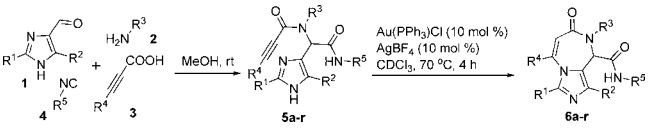
heteroannulation approach for the synthesis of imidazodiazepinones.

Ugi 4-CR[11] of imidazole-4-carbaldehyde (**1a**), *p*-methoxybenzylamine (**2a**), 2-butynoic acid (**3a**), and *tert*-butyl isonitrile (**4a**) in methanol at rt furnishes the corresponding Ugi adduct **5a** in 84% yield. This compound was used to check the feasibility of the intramolecular heteroannulation. The application of 10 mol % of AuCl or $AuCl_3$ as catalyst produced imidazodiazepinone **6a** in 100% conversion with a yield of 80 and 72%, respectively, while only 20% conversion was observed with $Au(PPh_3)Cl$ (Table 1, entries 1−3). The use of $Au(PPh_3)OTf$ (10 mol %) gave 100% conversion in 10 h with a yield of 96%, while only 60% conversion was observed with $Au(PPh_3)SbF_6$ after 24 h (Table 1, entries 4 and 5). $Au(PPh_3)BF_4$ (10 mol %) at 50 °C furnished 65% conversion, while heating at 70 °C resulted in 100% conversion in just 4 h with a yield of 98% (Table 1, entry 6 and 7). Also $Au(PPh_3)NTf_2$, $Au(X\text{-}Phos)NTf_2$, and with $Au(PPh_3)Cl$ (Table 1, entries 1−3). The use of $Au(PPh_3)OTf$ (10 mol %) gave 100% conversion in 10 h with a yield of 96%, while only 60% conversion was observed with $Au(PPh_3)SbF_6$ after 24 h (Table 1, entries 4 and 5). $Au(PPh_3)BF_4$ (10 mol %) at 50 °C furnished 65% conversion, while heating at 70 °C resulted in 100% conversion in just 4 h with a yield of 98% (Table 1, entry 6 and 7). Also $Au(PPh_3)NTf_2$, $Au(X\text{-}Phos)NTf_2$, and $[MeCN(JohnPhos)Au]SbF_6$ gave 100% conversion with excellent yields but with longer reaction times (Table 1, entries 8−10). Although the reaction with the comparitivily cheaper $AgBF_4$ was found to be feasible, a longer reaction time was required (Table 1, entry 11). No amelioration was observed with CuOTf, $Sc(OTf)_3$ or $Bi(OTf)_3$, (Table 1, entries 12−14). In the case of cationic gold-catalysis, changing the solvent into ACN-d_3 resulted in a decreased yield, while in THF-d_8 a lower conversion was obtained (Table 1, entries 15 and 16). Diminishing the catalyst loading to 5 mol % resulted in a decreased conversion (Table 1, entry 17). No conversion was obtained without catalyst (Table 1, entry 18).

To evaluate the scope and limitations of our optimized protocol (Table 1, entry 7), different Ugi adducts (**5a**−**r**) were synthesized from imidazole-4-carbaldehyde (**1a**) and subjected to the intramolecular heteroannulation reaction (Table 2). Various substituents related to the alkyne, the isonitrile, the imidazole, and the amine are tolerated giving good to excellent yields. A bulky substituent like a phenyl group on the alkyne consistently reduced the reaction rate, increasing the temperature to 80 °C and the time to 72 h with 20 mol % of catalyst loading, leading to an isolated yield of 82% (Table 2, **6e**). When the Ugi adduct containing a terminal alkyne was subjected to the optimized conditions, the exclusive formation of the *endo* product was observed in 75% isolated yield (Table 2, **6q**).

On the basis of previous investigations of related cyclizations,[2,10−13] a plausible mechanism for this gold(I)-catalyzed intramolecular heteroannulation reaction is depicted in Scheme 1. The coordination of the metal with the alkyne in the Ugi-adduct **5a** generates intermediate **A**. Nucleophilic attack of the imidazole on the activated

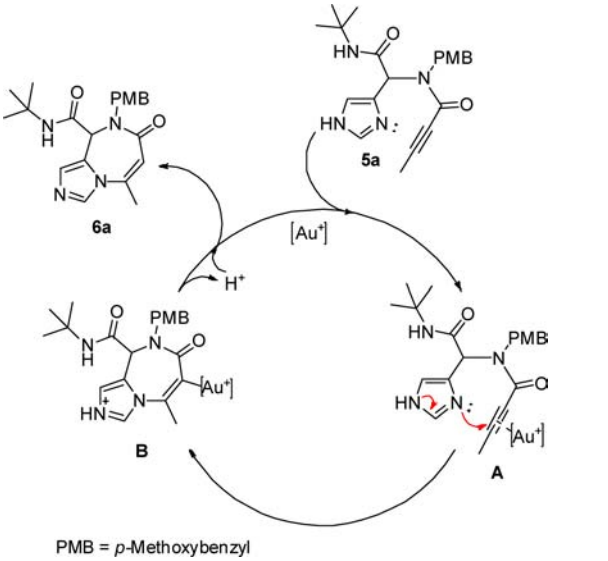
Table 2. Scope of the Intramolecular Heteroannulation Reaction[a]



						yield (%)	
entry	R^1	R^2	R^3	R^4	R^5	Ugi adduct (**5**)	imidazodiazepinone (**6**)
a	H	H	PMB	Me	*t*-Bu	84	98 (84)[b]
b	H	H	PMB	Me	Cy	82	94 (65)[b]
c	H	H	PMB	Me	*n*-Bu	75	90
d	H	H	PMB	Et	*t*-Bu	73	92
e	H	H	PMB	Ph	*t*-Bu	62	82[c]
f	H	Me	PMB	Me	Cy	54	79
g	H	H	piperonyl	Me	*t*-Bu	57	89
h	H	H	piperonyl	Et	*t*-Bu	63	93 (76)[b]
i	H	Me	piperonyl	Me	*t*-Bu	47	96 (68)[b]
j	H	H	piperonyl	Me	Cy	71	86 (74)[b]
k	H	H	3,4-DMB	Me	*t*-Bu	70	90 (81)[b]
l	H	Me	3,4-DMB	Me	Cy	50	96
m	H	H	3,4-DMB	Me	Cy	97	97
n	H	H	3,4-DMB	Et	Cy	63	82
o	H	Me	PMB	Me	*t*-Bu	63	95
p	H	H	Bn	Me	Cy	34	88
q	H	H	3,4-DMB	H	*t*-Bu	85	75
r	Me	H	PMB	Me	*t*-Bu	55	77

[a] All reactions were run on a 0.25 mmol scale of **5a** with $Au(PPh_3)BF_4$ (10 mol %) and $CHCl_3$ (2 mL) in a screw capped vial at 70 °C for 4 h. [b] The reaction was carried using $AgBF_4$ (10 mol %) at 70 °C for 24−30 h. [c] $Au(PPh_3)BF_4$ (20 mol %) was used at 80 °C for 72 h. 3,4-DMB = 3,4-dimethoxybenzyl.

Scheme 1. Plausible Mechanism for the Gold-Catalyzed Heteroannulation



alkyne occurs in an *endo-dig* fashion generating a 7-membered ring intermediate **B**, which upon deprotonation and protodeauration forms imidazodiazepinone **6a**.

In summary, we have elaborated a novel diversity-oriented approach for the synthesis of interesting imidazo-[1,4]diazepin-7-ones starting from readily available building blocks. The first step, the Ugi-4CR, generates diversity, while the second step, an efficient gold(I)-catalyzed hetero-annulation, results in the formation of the imidazo[1,4]-diazepin-7-one scaffold.

Acknowledgment. We thank the FWO [Fund for Scientific Research - Flanders (Belgium)] and the Research Fund of the University of Leuven (KU Leuven) for financial support. A.K. is thankful to EMA2experts (Erasmus Mundus Action 2, Lot 11 Asia: Experts) for providing a doctoral exchange scholarship, and Z.L. is thankful to the CSC (China Scholarship Council) for providing a doctoral scholarship.

Supporting Information Available. General experimental details and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.