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Synthesis of 3,4-dihydropyrrolo[2,1-*a*]isoquinolines based on [3+2] cycloaddition initiated by $Rh_2(cap)_4$-catalyzed oxidation

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ABSTRACT

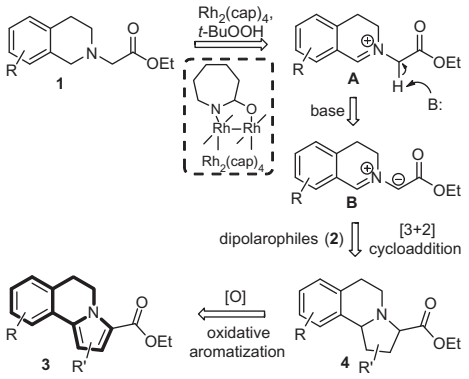
Azomethine ylides have been efficiently generated via $Rh_2(cap)_4$-catalyzed oxidation of tetrahydroisoquinoline derivatives in the presence of base. The ylides are trapped in situ via [3+2] cycloaddition with dipolarophiles and subjected to oxidative aromatization facilitated by *N*-bromosuccinimide to provide 3,4-dihydropyrrolo[2,1-*a*]isoquinoline derivatives in moderate to excellent yields.

Pyrrolo[2,1-*a*]isoquinoline, which occurs in lamellarin alkaloids,[1] serves as an important heterocyclic system and has attracted considerable attention in the synthetic organic community. Various approaches have been developed to synthesize this skeleton,[2] with transition metal-catalyzed tandem reactions being among the most efficient. For example, using $CuBr_2$ or Ru poly-pyridine complexes[3–5] as catalyst in conjunction with suitable oxidants allowed efficient construction of 3,4-dihydropyrrolo[2,1-*a*]isoquinoline derivatives from tetrahydroisoquinoline esters via dipolar cycloaddition of azomethine ylides, followed by oxidative aromatization. In this process, the catalytic oxidation protocol generated 3,4-dihydroisoquinolinium species, which served as precursors of the azomethine ylides.[6]

Pioneering work by Doyle has shown that an extremely effective way to generate iminium species is catalytic oxidation of tertiary amines using *tert*-butyl hydroperoxide (TBHP) in the presence of dirhodium(II) caprolactamate [$Rh_2(cap)_4$] catalyst.[7–12] Doyle has further demonstrated that iminium ions generated in situ in this way can be captured by 2-siloxyfurans via nucleophilic addition.[9] Our interest in dirhodium(II) complexes and their applications[13] led us to examine whether Doyle's oxidation protocol could be extended to a variant of dipolarophilic cycloaddition.

As shown in Scheme 1, we speculated that $Rh_2(cap)_4$-catalyzed oxidation of tetrahydroisoquinoline derivatives (**A**) could generate iminium ions, which could undergo base-facilitated deprotonation to produce azomethine ylides (**B**). The ylide intermediate **B** could then react with dipolarophiles (**2**) to give cycloadducts (**4**), which could be further oxidized to 3,4-dihydropyrrolo[2,1-*a*]isoquinoline derivatives (**3**). If successful, this approach would extend $Rh_2(cap)_4$/TBHP catalytic oxidation to [3+2] cycloaddition. Here, we report our preliminary results using this approach.

We optimized reaction conditions using the model reaction of ethyl 2-(3,4-dihydroisoquinolin-2(1*H*)-yl) acetate (**1a**) with *N*-phenylmaleimide (**2a**) (Table 1). Dipolar cycloaddition initiated by $Rh_2(cap)_4$-catalyzed oxidation proceeded quite slowly to give



Scheme 1. $Rh_2(cap)_4$-catalyzed oxidation initiates a cascade of iminium formation, dipolar cycloaddition, and oxidative aromatization.

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Table 1
Optimizing the reaction of **1a** with **2a**[a]

Entry	Catalyst loading (mol %)	Base (50 mol %)	Time (h)	Yield[b] (%) (**3a**/**4a**)
1	1	None	60	5/50
2[c]	1	None	60	57/0
3[c]	1	$NaHCO_3$	5	51/0
4[c]	1	K_2CO_3	3	63/0
5[c]	1	*i*-Pr_2NEt	3	49/0
6[c]	0.5	K_2CO_3	3.5	62/0
7[d]	0.5	K_2CO_3	4	97/0

[a] Reaction conditions: **1a** (0.36 mmol), **2a** (0.30 mmol), $Rh_2(cap)_4$, *t*-BuOOH (5.5 M in decane, 2.0 equiv), and CH_3CN (3.0 mL) at room temperature.
[b] Isolated yield after silica gel chromatography.
[c] *N*-Bromosuccinimide (2.0 equiv) was added to the reaction mixture at the indicated times, and stirring was continued for 1 h.
[d] **2a** was dissolved in CH_3CN (1.0 mL) and added slowly to the reaction mixture over 2 h using a syringe pump.

hexahydropyrrolo[2,1-*a*]isoquinoline **3a** in 5% yield and dihydropyrrolo[2,1-*a*]isoquinoline **4a** in 50% yield after 60 h (entry 1). Incorporating *N*-bromosuccinimide (NBS) oxidation[4] by adding NBS (2.0 equiv) to the reaction mixture after complete consumption of substrate **2a** gave **3a** as the only product in 57% yield (entry 2). Adding typical inorganic or organic bases (50 mol %) considerably shortened the reaction time from 60 to 3–5 h with comparable yields (entries 3–5). Moreover, catalyst loading could be reduced to 0.5 mol % without a notable decrease in yield (entry 6).[14] To our delight, **3a** was isolated in excellent yield (97%) when **2a** was added slowly over 2 h using a syringe pump (entry 7).[15] Reactions did not occur in the absence of $Rh_2(cap)_4$ or TBHP.

We examined the substrate scope of the cascade transformation using the optimized reaction conditions and various dipolarophiles **2** reported in Ref. 4 (Table 2).[16] Various N-substituted maleimides **2a**–**2e** reacted smoothly with **1a** to give the corresponding products **3a**–**3e** in moderate to excellent yields (entries 1–5). When

Table 2
Reaction of tetrahydroisoquinolines with dipolarophiles[a]

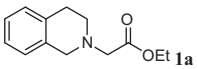
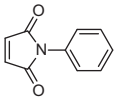
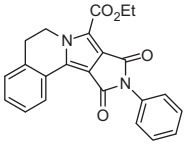
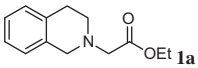
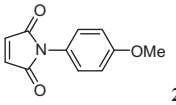
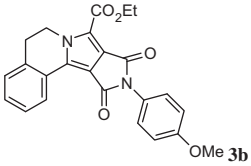
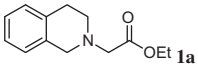
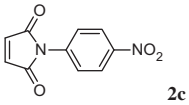
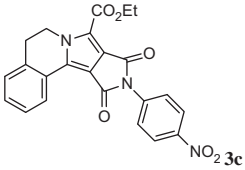
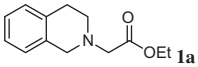
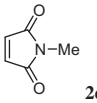
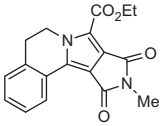
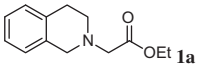
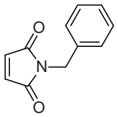
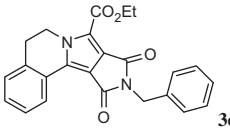
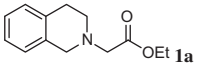
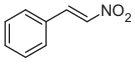
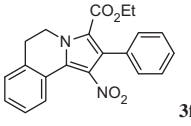
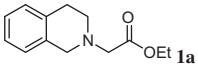
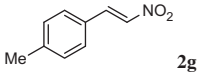
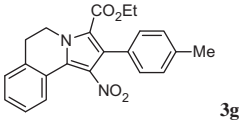
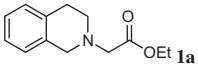
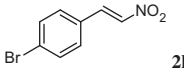
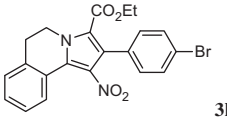
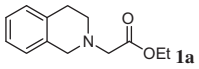
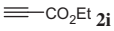
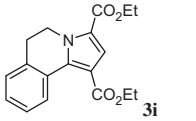
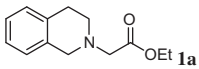
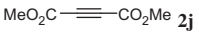
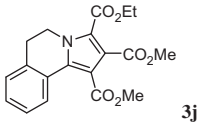
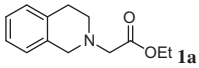
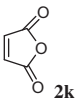
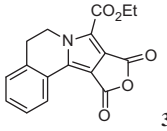
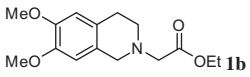
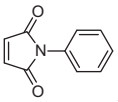
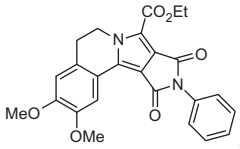
Entry	Dihydroisoquinoline	Dipolarophile	Product	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	97 (94)
2	 **1a**	 **2b**	 **3b**	95 (81)
3	 **1a**	 **2c**	 **3c**	97 (68)
4	 **1a**	 **2d**	 **3d**	76 (94)
5	 **1a**	 **2e**	 **3e**	69 (76)
6	 **1a**	 **2f**	 **3f**	57 (64)
7	 **1a**	 **2g**	 **3g**	48 (62)
8	 **1a**	 **2h**	 **3h**	46 (53)

Table 2 (*continued*)

Entry	Dihydroisoquinoline	Dipolarophile	Product	Yield[b] (%)
9	 **1a**	 **2i**	 **3i**	53 (52)
10	 **1a**	 **2j**	 **3j**	73 (65)
11	 **1a**	 **2k**	 **3k**	45 (51)
12	 **1b**	 **2a**	 **3l**	91 (89)

[a] Reaction conditions: **1a** (0.36 mmol), Rh2(cap)4 (1.1 mg, 0.5 mol %), *t*-BuOOH (0.60 mmol, 5.5 M in decane, 2.0 equiv), and K_2CO_3 (0.15 mmol, 50 mol %) were dissolved in CH_3CN (2.0 mL) at room temperature, and then **2a** (0.3 mmol) in CH_3CN (1.0 mL) was added slowly over 2 h using a syringe pump. When **2a** had been completely consumed, *N*-bromosuccinimide (2.0 equiv) was added to the reaction mixture, and stirring was continued for 1 h.

[b] Isolated yield; yields reported in Ref. 4 are given in parentheses.

nitroolefins **2f**–**2h** were used as starting materials, the corresponding products **3f**–**3h** were obtained in 46–57% yields (entries 6–8). The unsymmetrical dipolarophile **2i** gave the regioisomer **3i** exclusively (entry 9), while the reaction of symmetrical alkyne **2j** with tetrahydroisoquinoline **1a** yielded the desired adduct **3j** in 73% yield (entry 10). Maleic anhydrides **2k** showed low reactivity in the tandem reaction, giving 3,4-dihydropyrrolo[2,1-*a*]isoquinoline product **3k** in 45% yield (entry 11). The dihydroisoquinoline ester derivative **1b** reacted smoothly with **2a** to give **3l** in 91% yield (entry 12). The yields obtained using the protocol described here were comparable to those reported in Ref. 4 (Table 2, yields in parentheses), indicating that 3,4-dihydropyrrolo[2,1-a]isoquinolines can be synthesized effectively via [3+2] cycloaddition initiated by $Rh_2(cap)_4$-catalyzed oxidation. This approach can therefore be considered a proper alternative to the photocatalytic oxidation process based on Ru poly-pyridine complexes reported in Ref. 4.

In summary, we have developed an efficient cascade involving $Rh_2(cap)_4$-catalyzed oxidation, [3+2] cycloaddition, and oxidative aromatization, and we have used it to construct a variety of 3,4-dihydropyrrolo[2,1-*a*]isoquinoline derivatives. This approach uses Doyle's oxidative protocol to generate azomethine ylides and trap them in situ via dipolarophilic cycloaddition.

Acknowledgments

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References and notes

1. For recent reviews on lamellarins and related alkaloids, including their synthesis, see: (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264; (b) Pla, D.; Albericio, F.; Alvarez, M. *Anti-Cancer Agents Med. Chem.* **2008**, *8*, 746; (c) Pla, D.; Albericio, F.; Alvarez, M. *Med. Chem. Commun.* **2011**, *2*, 689; (d) Fukuda, T.; Ishibashi, F.; Iwao, M. *Heterocycles* **2011**, *83*, 491.
2. For representative examples, see: (a) Heim, A.; Terpin, A.; Steglich, W. *Angew. Chem., Int. Ed.* **1997**, *36*, 155; (b) Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259; (c) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54; (d) Ridley, C. P.; Reddy, M. V. R.; Rocha, G.; Bushman, F. D.; Faulkner, D. J. *Bioorg. Med. Chem.* **2002**, *10*, 3285; (e) Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 866; (f) Cironi, P.; Manzanares, I.; Albericio, F.; Alvarez, M. *Org. Lett.* **2003**, *5*, 2959; (g) Handy, S. T.; Zhang, Y. N.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362; (h) Ploypradith, P.; Kagan, R. K.; Ruchirawat, S. *J. Org. Chem.* **2005**, *70*, 5119; (i) Hamasaki, A.; Zimpleman, J. M.; Hwang, I.; Boger, D. L. *J. Am. Chem. Soc.* **2005**, *127*, 10767; (j) Ploypradith, P.; Petchmance, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440; (k) Su, S.; Porco, A. J., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744; (l) Gupton, J. T.; Banner, E. J.; Sartin, M. D.; Coppock, M. B.; Hempel, J. E.; Kharlamova, A.; Fisher, D. C.; Giglio, B. C.; Smith, K. L.; Keough, M. J.; Smith, T. M.; Kanters, R. P. F.; Dominey, R. N.; Sikorski, J. A. *Tetrahedron* **2008**, *64*, 5246; (m) Ohta, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *J. Org. Chem.* **2009**, *74*, 8143; (n) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138; (o) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2011**, *13*, 312; (p) Ackermann, L.; Wang, L.; Lygin, A. V. *Chem. Sci.* **2012**, *3*, 177.
3. For catalytic oxidation using $CuBr_2$, see: Yu, C.; Zhang, Y.; Zhang, S.; Li, H.; Wang, W. *Chem. Commun.* **2011**, 1036.
4. For catalytic oxidation using Ru poly-pyridine complexes, see: Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171. and Ref. 5.
5. Rueping, M.; Leonori, D.; Poisson, T. *Chem. Commun.* **2011**, 9615.
6. Huisgen, R.; Grashey, R.; Steingruber, E. *Tetrahedron Lett.* **1963**, *4*, 1441.
7. For $Rh_2(cap)_4$-catalyzed allylic oxidation, see: (a) Catino, A. J.; Forslund, R. E.; Doyle, M. P. *J. Am. Chem. Soc.* **2004**, *126*, 13622; (b) Choi, H.; Doyle, M. P. *Org. Lett.* **2007**, *9*, 5349; (c) McLaughlin, E. C.; Choi, H.; Wang, K.; Chiou, G.; Doyle, M. P. *J. Org. Chem.* **2009**, *74*, 730.
8. For $Rh_2(cap)_4$-catalyzed benzylic oxidation, see: Catino, A. J.; Nichols, J. M.; Choi, H.; Gottipamula, S.; Doyle, M. P. *Org. Lett.* **2005**, *7*, 5167.
9. For $Rh_2(cap)_4$-catalyzed oxidation of tertiary amines to initiate the Mannich reaction, see: Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. *J. Am. Chem. Soc.* **2006**, *128*, 5648.
10. For $Rh_2(cap)_4$-catalyzed oxidation of secondary amines, see: Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745.
11. For $Rh_2(cap)_4$-catalyzed propargylic oxidation, see: McLaughlin, E. C.; Doyle, M. P. *J. Org. Chem.* **2008**, *73*, 4317.
12. For $Rh_2(cap)_4$-catalyzed oxidation of phenol and aniline, see: Ratnikov, M. O.; Farkas, L. E.; McLaughlin, E. C.; Chiou, G.; Choi, H.; El-Khalafy, S. H.; Doyle, M. P. *J. Org. Chem.* **2011**, *76*, 2585.
13. (a) Tusun, X.; Lu, C.-D. *Synlett* **2012**, 1801; (b) Wusiman, A.; Tusun, X.; Lu, C.-D. *Eur. J. Org. Chem.* **2012**, 3088.
14. Further reductions in catalyst loading decreased yields and prolonged reaction times. For example, performing the reaction with 0.1 mol % catalyst loading afforded **3a** in 37% yield after 24 h.
15. The reasons for the improvement resulted from slow introduction of substrate **2a** on the reaction are unclear.
16. *General experimental procedure:* $Rh_2(cap)4{\cdot}2CH_3CN$ (0.0015 mmol), tetrahydroisoquinoline 1 (0.36 mmol), and K_2CO_3 (0.15 mmol) in CH_3CN (2.0 mL) were mixed and kept under stirring while *t*-BuOOH (5.5 M in decane, 0.60 mmol) was added in one portion at room temperature. Then *N*-

phenylmaleimide 2 (0.30 mmol) in CH_3CN (1.0 mL) was added dropwise over 2 h using a syringe pump. The reaction was stirred until substrate 2 was completely consumed (ca. 3 h), and then *N*-bromosuccinimide (0.60 mmol) was added and stirring continued for 1 h. Saturated $NaHSO_3$ (5 mL) was added to quench the reaction. The crude mixture was extracted with CH_2Cl_2 (10 mL $\times$3), and the combined organic phases were dried over sodium sulfate and filtered. The filtrate was concentrated and the residue purified by flash column chromatography on silica gel using petroleum ether-dichloromethane-ethyl acetate as the eluent, giving the desired product **3**. The structures of the cycloadducts **3a**–**l** were identified by comparison with the ^1H NMR spectra in Ref. 4 and confirmed by mass spectra.