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The Dual Role of Ruthenium and Alkali Base Catalysts in Enabling a Conceptually New Shortcut to *N*-Unsubstituted Pyrroles through Unmasked α-Amino Aldehydes

Kazuki Iida,[†] Takashi Miura,[†] Junki Ando,[†] and Susumu Saito*[,†,‡]

Graduate School of Science, Nagoya University, Chikusa, Nagoya 464-8602, Japan, and Institute for Advanced Research, Nagoya University, Chikusa, Nagoya 464-8601, Japan

saito.susumu@f.mbox.nagoya-u.ac.jp

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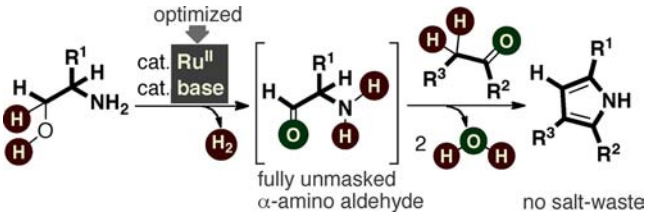
ABSTRACT



A virtually salt-free and straightforward bimolecular assembly giving *N*-unsubstituted pyrroles through fully unmasked α-amino aldehydes, which was enabled by the dual effects of a catalytic ruthenium complex and an alkali metal base, is reported. Either solvent-free or acceptorless dehydrogenation facilitates high atom, step, and pot economy, which are otherwise difficult to achieve in multistep operations involving protection/deprotection.

Fully unmasked α-amino aldehydes (α-AMALs) are notoriously unstable synthetic intermediates and have rarely been used in organic synthesis.[1] For example, rapid degradation of valinal is accompanied by self-dimerization giving the symmetric pyrazine.[2] To avoid such shortcomings, *N*-protected[3] and *C*-protected[4] α-AMALs have been isolated and are widely used in natural product synthesis and asymmetric catalysis. Were it possible to generate an unmasked α-AMAL in conjunction with its reaction partner and subsequently incorporate them into products without isolation of the α-AMALs, the atom- step-, and pot-economical utility would be increased significantly. In particular, the transition-metal-catalyzed "hydrogen autotransfer" strategy[5]—transfer dehydrogenation of an unprotected *β*-amino alcohol, followed by in situ trapping of the resulting α-AMAL with a carbon nucleophile—would benefit from the advanced synthetic utility of α-AMALs. We[6] and others[7,8] have demonstrated that, even under basic conditions, aliphatic linear aldehydes thus generated in situ undergo negligible aldol self-condensation. Reported herein is the virtually salt-free and highly versatile synthesis of *N*-unsubstituted pyrroles using a catalytic ruthenium complex **1**[9] (Figure 1) and an alkali

[†] Graduate School of Science.
[‡] Institute for Advanced Research.

(1) (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (b) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825. (c) Gryko, D.; Chalko, J.; Jurczak, J. *Chirality* **2003**, *15*, 514.

(2) (a) Badrinarayanan, S.; Sperry, J. *Org. Biomol. Chem.* **2012**, *10*, 2126. (b) Badrinarayanan, S.; Sperry, J. *Synlett* **2011**, 2339.

(3) (a) Reetz, M. T. *Angew. Chem., Int. Ed.* **1991**, *30*, 1531. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121. Recent examples: (c) Nakano, A.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Org. Lett.* **2006**, *8*, 5357. (d) Restorp, P.; Fischer, A.; Somfai, P. *J. Am. Chem. Soc.* **2006**, *128*, 12646. (e) Soto-Cairoli, B.; Soderquist, J. A. *Org. Lett.* **2009**, *11*, 401.

(4) (a) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401. (b) Kwon, S.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 16796. (c) Tian, J.-S.; Loh, T.-P. *Chem. Commun.* **2011**, *47*, 5458.

(5) Recent reviews: (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555. (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681.

(6) (a) Miura, T.; Kose, O.; Li, F.; Sun, K.; Saito, S. *Chem.—Eur. J.* **2011**, *17*, 11146. (b) Kose, O.; Saito, S. *Org. Biomol. Chem.* **2010**, *8*, 896.

(7) Ir and/or Ru; recent examples: (a) Onodera, G.; Nishibayashi, Y.; Uemura, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 3819. (b) Viciano, M.; Sanaú, M.; Peris, E. *Organometallics* **2007**, *26*, 6050. (c) Gnanamgari, D.; Leung, C. H.; Schley, N. D.; Hilton, S. T.; Crabtree, R. H. *Org. Biomol. Chem.* **2008**, *6*, 4442. (d) Gnanamgari, D.; Sauer, E. L. O.; Schley, N. D.; Butler, C.; Incarvito, C. D.; Crabtree, R. H. *Organometallics* **2009**, *28*, 321. (e) Chang, X.; Chuan, L. W.; Yongxin, L.; Pullarkat, S. A. *Tetrahedron Lett.* **2012**, *53*, 1450.

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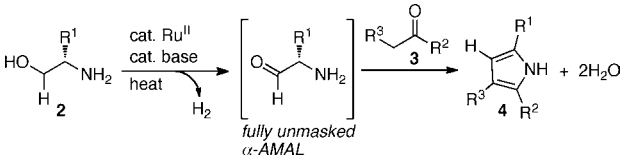
metal base, in which readily available and easily varied ketones (enolates) react with α-AMALs generated in situ from fully unmasked β-amino alcohols (Scheme 1). Recently, elegant progress has been made based on multicomponent coupling[10a,c,11] and preassembled specialty building blocks for intra-[12] and intermolecular[13] cyclization, providing pyrrole structures[10,14] not easily generated via classical routes. The present approach is simpler and more straightforward than these established methods.[15]

"Hydrogen autotransfer" starting from transfer dehydrogenation of alcohols followed by a cross aldol reaction is usually carried out using a transition-metal catalyst based on Ru,[7] Ir,[7] Ni,[8a] Pd,[6b,8b] Ag,[8c] Cu,[6a,8d,8e] Fe,[8f] or Au[8g] in the presence of a catalytic or stoichiometric alkali metal base. Nontransition-metal-based systems, catalytic NaOH/H_2-,[6a] KOH (or NaOH)/air-[16a] and stoichiometric KOBu^t-promoted versions,[16b,c] can also be effective. However, detailed studies are lacking as to which, the transition metal species or the base, is more responsible for the catalysis. Thus, this issue was reconsidered using a new ruthenium complex **1** (Figure 1) we recently introduced[9] as a multifunctional catalyst precursor able to achieve the reverse processes, namely, the hydrogenation of unactivated amides[9] and ketones. Catalyst precursor **1** is readily available in two steps from commercial resources.[17]

Scheme 1. Basic Strategy of the Catalytic, Salt-Free, Bimolecular Reaction, Which Affords an *N*-Unsubstituted Pyrrole via a Fully Unmasked α-AMAL



At the outset, a 1:2 molar ratio of valinol (**2a**) to propiophenone (**3a**) was subjected to catalytic **1** and KOBu^t in toluene to synthesize pyrrole **4aa**. The effects of several

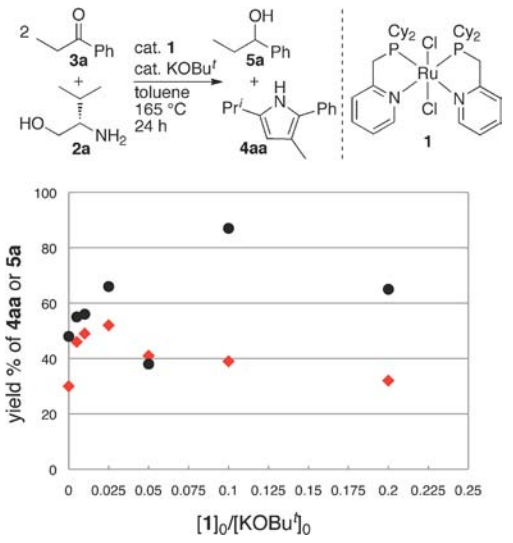


Figure 1. ^{1}H NMR yield (%) of **4aa** and **5a** as a function of $[1]_0/[KOBu^t]_0$ at $[KOBu^t]_0$ = 74 mM. Data points were obtained from the reactions as shown above the figure. (●) **5a**. (◆, red) **4aa**.

factors, namely $[1]_0$ (0−15 mM: 0−2 mol % relative to **2a**), $[KOBu^t]_0$ (25, 37, 60, and 74 mM: 10 mol % each), and $[KOBu^t]_0/[1]_0$ (1/0 to 100/1), on the yields of **4aa** were investigated. A plot of $[1]_0/[KOBu^t]_0$ vs yield % of **4aa** at

(8) Ni: (a) Alonso, F.; Riente, P.; Yus, M. *Eur. J. Org. Chem.* **2008**, 4908. Pd: (b) Kwon, M. S.; Kim, N.; Seo, S. H.; Park, I. S.; Cheedrala, R. K.; Park, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 6913. Ag: (c) Shimizu, K.; Sato, R.; Satsuma, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 3982. Cu: (d) Liao, S.; Yu, K.; Li, Q.; Tian, H.; Zhang, Z.; Yu, X.; Xu, Q. *Org. Biomol. Chem.* **2012**, *10*, 2973. (e) Cho, C. S.; Ren, W. X.; Yoon, N. S. *J. Mol. Catal. A: Chem.* **2009**, *299*, 117. Fe: (f) Yang, J.; Liu, X.; Meng, D.-L.; Chen, H.-Y.; Zong, Z.-H.; Feng, T.-T.; Sun, K. *Adv. Synth. Catal.* **2012**, *354*, 328. Au: (g) Kim, S.; Bae, S. W.; Lee, J. S.; Park, J. *Tetrahedron* **2009**, *65*, 1461.

(9) The present results and **1** were primarily submitted as a patent: (a) Saito, S.; Noyori, R.; Miura, T.; Held, I. E.; Suzuki, M.; Iida, K. JP patent Appl. #2011-012316, Filed: Jan. 24, 2011. (b) Miura, T.; Held, I. E.; Oishi, S.; Saito, S. *Catalysts and Catalysis* **2012**, *54*, 455.

(10) Reviews: (a) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. (b) Schmuck, C.; Rupprecht, D. *Synthesis* **2007**, 3095. (c) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402.

(11) Recent multicomponent coupling in one pot: (a) Zhang, M.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 597. (b) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088. (c) Reddy, G. R.; Reddy, T. R.; Joseph, S. C.; Reddy, K. S.; Pal, M. *RSC Adv.* **2012**, *2*, 3387. (d) Lin, X.; Mao, Z.; Dai, X.; Lu, P.; Wang, Y. *Chem. Commun.* **2011**, *47*, 6620. (e) Hong, D.; Zhu, Y.; Li, Y.; Lin, X.; Lu, P.; Wang, Y. *Org. Lett.* **2011**, *13*, 4668. (f) Wang, T.; Chen, X.; Chen, L.; Zhan, Z. *Org. Lett.* **2011**, *13*, 3324.

(12) Recent intramolecular cyclization: (a) Xin, X.; Wang, D.; Li, X.; Wan, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 1693. (b) Jiang, Y.; Chan, W. C.; Park, C.-M. *J. Am. Chem. Soc.* **2012**, *134*, 4104. (c) Mo, D.-L.; Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Chem.—Asian J.* **2011**, *6*, 3200. (d) Sharland, C. M.; Singkhonrat, J.; NajeebUllah, M.; Hayes, S. J.; Knight, D. W.; Dunford, D. G. *Tetrahedron Lett.* **2011**, *52*, 2320. (e) Donohoe, T. J.; Race, N. J.; Bower, J. F.; Callens, C. K. A. *Org. Lett.* **2010**, *12*, 4094.

(13) Recent intermolecular cyclization: (a) Zhang, M.; Zhang, J. *Chem. Commun.* **2012**, *48*, 6399. (b) Zhang, Y.-Q.; Zhu, D.-Y.; Li, B.-S.; Tu, Y.-Q.; Liu, J.-X.; Lu, Y.; Wang, S.-H. *J. Org. Chem.* **2012**, *77*, 4167. (c) Khlebnikov, A. F.; Golovkina, M. V.; Novikov, M. S.; Yufit, D. S. *Org. Lett.* **2012**, *14*, 3768. (d) Zhao, M.; Wang, F.; Li, X. *Org. Lett.* **2012**, *14*, 1412. (e) Huestis, M. P.; Chan, L.; Stuart, D. R.; Fagnou, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 1338. (f) Palmieri, A.; Gabrielli, S.; Cimarelli, C.; Ballini, R. *Green Chem.* **2011**, *13*, 3333. (g) Ng, E. P. J.; Wang, Y.-F.; Hui, B. W.-Q.; Lapointe, G.; Chiba, S. *Tetrahedron* **2011**, *67*, 7728. (h) Trost, B. M.; Lumb, J.-P.; Azzarelli, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 740. (i) Wang, Y.; Bi, X.; Li, D.; Liao, P.; Wang, Y.; Yang, J.; Zhang, Q.; Liu, Q. *Chem. Commun.* **2011**, *47*, 809.

(14) Of pharmaceutical importance: (a) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54. (b) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (c) Hughes, C. C.; Prieto-Davo, A.; Jensen, P. R.; Fenical, W. *Org. Lett.* **2008**, *10*, 629. (d) Davis, J. T.; Gale, P. A.; Okunola, O. A.; Prados, P.; Iglesias-Sánchez, J. C.; Torroba, T.; Quesada, R. *Nat. Chem.* **2009**, *1*, 138. (e) Khan, A. T.; Lal, M.; Bagdi, P. R.; Basha, R. S.; Saravanan, P.; Patra, S. *Tetrahedron Lett.* **2012**, *53*, 4145. Lipitor: (f) Graul, A.; Castañer, J. *Drugs Future* **1997**, *22*, 956. In materials science: (g) Novák, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev.* **1997**, *97*, 207. (h) Lee, D.; Swager, T. M. *J. Am. Chem. Soc.* **2003**, *125*, 6870. (i) Loudet, A.; Burgess, K. *Chem. Rev.* **2007**, *107*, 4891. (j) Wu, D.; Descalzo, A. B.; Weik, F.; Emmerling, F.; Shen, Z.; You, X.-Z.; Rurack, K. *Angew. Chem., Int. Ed.* **2008**, *47*, 193. (k) Takase, M.; Yoshida, N.; Narita, T.; Fujio, T.; Nishinaga, T.; Iyoda, M. *RSC Adv.* **2012**, *2*, 3221.

(15) In the meantime, amino alcohol−alcohol coupling for pyrrole synthesis using catalytic Ir complex and stoichiometric KOBu^t was reported: Michlik, S.; Kempe, R. *Nat. Chem.* **2013**, *5*, 140.

(16) (a) Allen, L. J.; Crabtree, R. H. *Green Chem.* **2010**, *12*, 1362–1364. Synthesis of quinolines from 2-(hydroxymethyl)anilines: (b) Martínez, R.; Ramón, D. J.; Yus, M. *J. Org. Chem.* **2008**, *73*, 9778. (c) Mierde, H. V.; Voort, P. V. D.; Verpoort, F. *Tetrahedron Lett.* **2008**, *49*, 6893.

(17) See Supporting Information.

$[KOBu^t]_0$ = 74 mM results in a bell-shaped curve giving a maximum yield of **4aa** at a specific value of $[KOBu^t]_0/[\mathbf{1}]_0$ (Figure 1; for other $[KOBu^t]_0$, see Figures S3−S6). The $[KOBu^t]_0/[\mathbf{1}]_0$ ratio was more critical than the $[\mathbf{2a}]_0$ or $[\mathbf{3a}]_0$ to the reaction rate in the dehydrogenation of **2a** (which corresponds to the yield of **5a**) and to an increase in the apparent overall reaction rate leading to **4aa** (Figures 1, S3, and S4). The $[KOBu^t]_0/[\mathbf{1}]_0$ ratio which gives the best yield of **4aa** is between 20 and 40 (Figures 1, S3, and S4). To obtain **4aa** in higher yields in the presence of **1** (than in its absence), $[KOBu^t]_0$ should be higher than 37 mM. Without **1**, the yield of pyrrole **4aa** averaged around 30%. In contrast, when $[KOBu^t]_0$ was 25 mM, the best yield of **4aa** (~40%) was obtained without **1** (0.25−2 mol %). The addition of **1** was detrimental to the production of **4aa** (Figure S5). In any event, the dual effects of the ruthenium and alkali metal base catalysts are obvious within the range of effective $[KOBu^t]_0$ for enhancement of product yield.

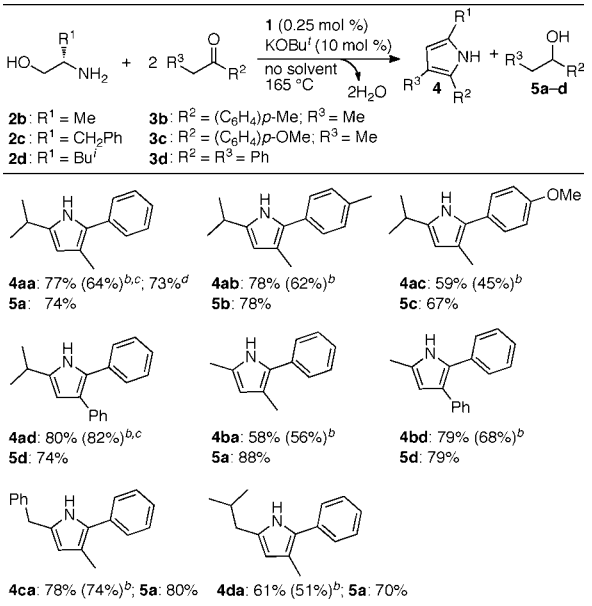
One of the characteristics of the reaction involving **2a** and **3a** is that, at a higher concentration of $[KOBu^t]_0$ (74 mM), a $[KOBu^t]_0/[\mathbf{1}]_0$ of 40 ($[\mathbf{1}]_0$ = 1.9 mM) gave the highest yield of **4aa** (52%) with **5a**/**4aa** = ~1.2. The amounts of **4aa** and of H_2 trapped by **3a** (corresponding to the yield of **5a**) were almost equal, so that, under these conditions, the performance of the transfer dehydrogenation directly reflects the efficiency of the conversion of the in situ generated α-AMAL to **4aa**. Therefore, a $[KOBu^t]_0$ > 37 mM and $[KOBu^t]_0/[\mathbf{1}]_0$ of 40 were chosen for further screening.

Among the higher concentrations of $[KOBu^t]_0$ tested, nonsolvent (neat) conditions ($[KOBu^t]_0$ = ca. 260 mM; $[\mathbf{1}]_0$ = 6−7 mM) afforded the highest yield of **4aa** (77%) (Table 1). Not more than 1 out of 2 equiv of **3a** relative to **2a** should be required to work as the H_2 acceptor; in fact, a 1:1 mixture of **2a** and **3a** gave **4aa** in lower yield (46%). Further screening of different amino alcohols **2a**−**d** and simple ketones **3a**−**d** shows that the reactions generally complete within 6−24 h, demonstrating the structural diversity of trisubstituted pyrroles. When other ruthenium complexes, such as $CpRuCl(PPh_3)_2$ (0.25 mol %) and $[(p\text{-Cymene})RuCl_2]_2$ (0.125 mol %), were reacted for 6 h in place of **1** under the regular conditions, **4aa** was obatined in lower yields (49% and 32%, respectively).

The reaction of **2a** with **3e** that gives 2,5-disubstituted pyrrole **4ae** was unselective under the solvent-free conditions. Rather, a more dilute toluene solution, with $[KOBu^t]_0$ = ca. 90 mM and $[\mathbf{1}]_0$ = 2−3 mM (1 mol %), was promising for the prevention of the self-dimerization of **3e** (Table 2). The reactions were nearly complete within 3 h. A 1−1.5:1 ratio of **2a**−**c** to **3e**−**g** gave more reasonable yields of the pyrroles, enabling the acceptorless dehydrogenation[18] followed by a bimolecular reaction. Evolution of H_2 was detected in all cases by micro-GC analysis. Even excess ketone (**2a:3e** = 1:2; $[KOBu^t]_0$ = ca. 90 mM) was unsatisfactory in functioning as an H_2 acceptor, and in fact, only a small amount of the α-phenethyl alcohol (~5%) derived from **3e** was detected by ^1H NMR. Without **3** under otherwise identical reaction conditions, ca. 20% of **2a** was detected as the dimer of the corresponding α-AMAL, pyrazine.[2a,19] Solvent-free conditions (**1**: 0.25 mol %; KO-Bu^t: 10 mol %) were employable for a bulky ketone **3h**, since, even with the higher concentration of **3h**, its aldol self-condensation was undetected.

The versatile nature of this approach was further demonstrated by the shortest and simplest access to the core pyrrole (**4ai**) of Lipitor (Atorvastatin Calcium)[14f] from the natural resource and 2,3,4,5-tetraphenyl-1*H*-pyrrole[20] (**4ed**) (Scheme 2), which was obtained in isolated yields of 33% and 16%, respectively. In these cases, **4ai** and **4ed** were not formed without using **1**, as ascertained by ^1H NMR. **4ai** was synthesized previously in a more tedious multistep[12e] reaction or via three-component coupling[11a] prior to being converted to Lipitor through a few synthetic steps.[12e]

Table 1. Synthesis of 2,3,5-Trisubstituted Pyrroles **4**[a]



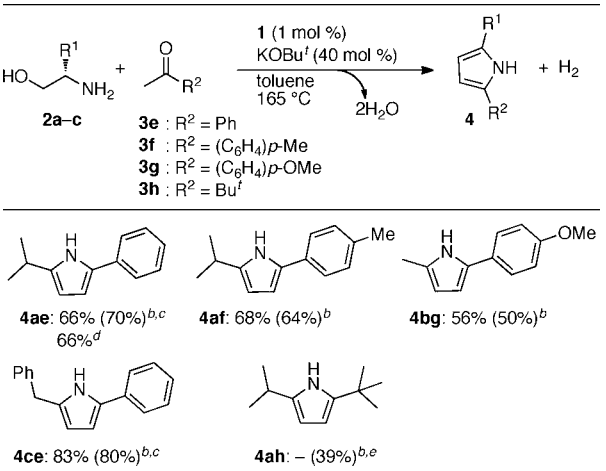
[a] Unless otherwise specified, the solvent-free reaction was carried out at 165 °C for 24 h under N_2 with $[KOBu^t]_0$ = ca. 260 mM; $[KOBu^t]_0/[\mathbf{1}]_0$ = 40; **1**/$KOBu^t$/**2**/**3** = 1:40:400:800. [b] Based on **2**, determined by ^1H NMR before $NaBH_4$ treatment. The values in parentheses are of isolated, purified products **4**, which were obtained after the final mixture was treated with $NaBH_4$ for the reduction and facial removal of the remaining **3**. [c] **4** was isolated without $NaBH_4$ treatment. [d] Reaction time: 6 h.

(18) (a) Musa, S.; Shaposhnikov, I.; Cohen, S.; Gelman, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 3533. (b) Fujita, K.; Yoshida, T.; Imori, Y.; Yamaguchi, R. *Org. Lett.* **2011**, *13*, 2278. (c) Ho, H.-A.; Manna, K.; Sadow, A. D. *Angew. Chem., Int. Ed.* **2012**, *51*, 8607. (d) Kawahara, R.; Fujita, K.; Yamaguchi, R. *Angew. Chem., Int. Ed.* **2012**, *51*, 12790.

(19) In contrast, transfer dehydrogenation of simple 2° alcohols using **1** was sluggish or nonselective. A solvent-free reaction of **5a** with **1** (0.25 mol %) and $KOBu^t$ (10 mol %) at 165 °C for 6 h gave **3a** in 44% yield (conversion of **5a**: 46%). Conversion of α-phenethyl alcohol (without using **2**) at 3 h under reaction conditions similar to those noted in Table 2 was >95%; however self-aldol condensation of **3e** and subsequent transfer hydrogenation of the α,β-unsaturated bond predominated.

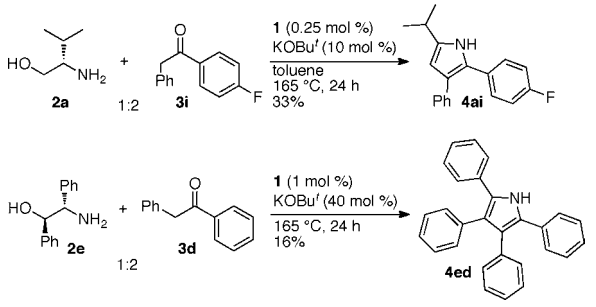
(20) (a) Gürdere, M. B.; Budak, Y.; Ceylan, M. *Asian J. Chem.* **2008**, *20*, 1425. (b) Kuo, W.-J.; Chen, Y.-H.; Jeng, R.-J.; Chan, L.-H.; Lin, W.-P.; Yang, Z.-M. *Tetrahedron* **2007**, *63*, 7086. (c) Ban, I.; Sudo, T.; Taniguchi, T.; Itami, K. *Org. Lett.* **2008**, *10*, 3607. (d) Feng, X.; Tong, B.; Shen, J.; Shi, J.; Han, T.; Chen, L.; Zhi, J.; Lu, P.; Ma, Y.; Dong, Y. *J. Phys. Chem. B* **2010**, *114*, 16731. (e) Liao, Q.; Zhang, L.; Wang, F.; Li, S.; Xi, C. *Eur. J. Org. Chem.* **2010**, 5426.

Table 2. Synthesis of 2,5-Disubstituted Pyrroles **4**[a]



[a] Unless otherwise specified, the reaction was carried out in toluene for 3 h under N_2 with $[KOBu^t]_0$ = ca. 90 mM; $[KOBu^t]_0/[\mathbf{1}]_0$ = 40; **1**/KOBu^t/**2**/**3** = 1:40:150:100. [b] Based on **3**, determined by ^{1}H NMR. The values in parentheses are of isolated, purified products **4**. [c] 24 h instead of 3 h. [d] **2a:3e** = 1:1. [e] Reaction conditions: those described in footnote *a* in Table 1.

Scheme 2. Synthesis of the Core Pyrrole of Lipitor and 2,3,4,5-Tetraphenyl-1*H*-pyrrole



The overall process of the pyrrole synthesis may derive from either one of two alternative steps (Figure 2): one begins with the dehydrogenation of a β-amino alcohol, followed by an intermolecular aldol reaction (path *a*); the other begins with the dehydrative formation of *N*,*O*-acetal **7** (path *b*).

To verify which pathway would be more likely, control experiments were carried out by separately preparing *N*,*N*-dibenzylated **2f** (R^4 = CH_2Ph, Scheme 3) and *N*,*O*-acetal **7** (R^3 = Me). The reaction of **2f** or **7** (with or without H_2O) with **3a** (165 °C, 24 h) proceeded in a different fashion to give **4fa** and **4aa** in ~40% (Scheme 3) and 0–10% yields, respectively. The transfer hydrogenation of the olefin of

(21) When a mixture of **2a** and **3a** in a 1:2 molar ratio was heated at 165 °C under solvent-free conditions for 1 h in the absence of **1** and KOBu^t, conversion of **2a** was 70%, giving **7** in 66% yield. In contrast, conversion of **2a** at 1 h was 91%, giving **4aa** in 42% yield and **7** in 13% yield under otherwise identical conditions noted in Table 1.

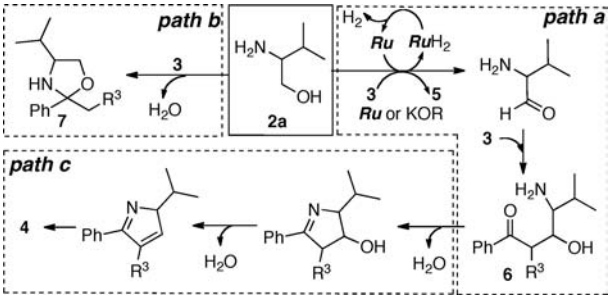
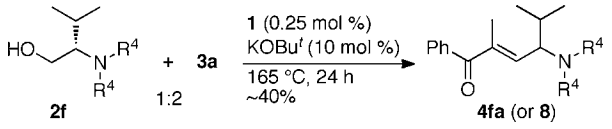


Figure 2. Possible divergent processes and most likely reaction pathways *a* and *c*. ***Ru*** denotes speculative catalytic species such as $(L_nRu^{2+})\bullet[(^-OR)_2(KOR)_n]$.

4fa was only slightly detected by FAB-MS analysis. This nature is different from that reported in other "hydrogen autotransfer" reactions involving transfer hydrogenation of α,β-unsaturated bonds (without O_2) as a major pathway.[7,8] Although path *b* could not be fully ruled out,[21] path *a*, transfer dehydrogenation followed by C–C bond formation, would be a more plausible initial step, accordingly. Since the molar amount of **5** generated (Table 1) and of H_2 evolved during the formation of **4af** and **4bg** (44% and 52% of H_2 relative to **3**, respectively, Table 2) were comparable with the amount of **4** produced, the process in which H_2 is removed from **2a** and subsequently incorporated into speculative **8** (R^4 = H, Scheme 3) is negligible. The borrowed hydrogen(s) rarely returned to **4fa** in the control experiment. All these results support path *c* as the major contribution.

Scheme 3. Control Experiment to Elucidate the Reaction Pathway



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Supporting Information Available. Experimental procedures, spectroscopic and analytical data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.