ORGANIC LETTERS

2012
Vol. 14, No. 10
2496–2499

Three-Component Organocascade Kinetic Resolution of Racemic Nitroallylic Acetates via Sequential Iminium/Enamine Asymmetric Catalysis

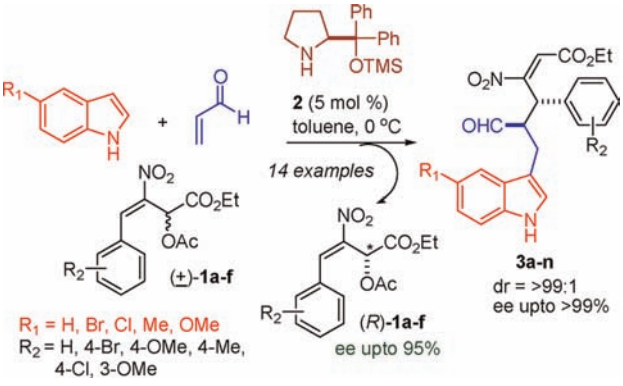
Suparna Roy and Kwunmin Chen*

Department of Chemistry, National Taiwan Normal University, Taipei, Taiwan 116, ROC

kchen@ntnu.edu.tw

Received March 27, 2012

ABSTRACT



Nitroallylic acetates 1a−f have been kinetically resolved via an asymmetric three-component coupling that involves indoles, acrolein, and nitroolefin allylic acetates and is mediated by the chiral catalyst 2 (5 mol %). The reactions proceed via iminium/enamine cascade catalysis. Both recovered starting substrates and reaction products are typically obtained in high chemical yield and in good to excellent enantiopurity (79−95% ee for 1a−f and 83−99% ee for 3a−n). For the first time, a highly efficient three-component, organocascade kinetic resolution has been demonstrated.

Kinetic resolution (KR) is now an established technique for the preparation of optically pure enantiomers from racemic mixtures.[1] Apart from traditional enzyme-mediated kinetic resolution, numerous metal-catalyzed processes have also been devised for this purpose,[2] and in recent years, there has been substantial interest in the development of organocatalytic asymmetric methods[3] for performing kinetic resolution, but so far success has

(1) For recent reviews, see: (a) Cardona, F.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2001**, 2999. (b) Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal.* **2001**, *343*, 5. (c) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (d) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron: Asymmetry* **2003**, *14*, 1407. (e) Vedejs, E.; Jure, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 3974.

(2) For selected references on metal-mediated kinetic resolution, see: (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237. (b) Gilbertson, S. R.; Lan, P. *Org. Lett.* **2001**, *3*, 2237. (c) Naasz, R.; Arnold, L. A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 927. (d) Ohkuma, T.; Koizumi, M.; Muñiz, K.; Hilt, G.; Kabuto, C.; Noyori, R. *J. Am. Chem. Soc.* **2002**, *124*, 6508. (e) Gayet, A.; Bertilsson, S.; Andersson, P. G. *Org. Lett.* **2002**, *4*, 3777. (f) Faller, J. W.; Wilt, J. C.; Parr, J. *Org. Lett.* **2004**, *6*, 1301. (g) Suárez, A.; Downey, C. W.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 11244. (h) Soeta, T.; Selim, K.; Kuriyama, M.; Tomioka, K. *Tetrahedron* **2007**, *63*, 6573. (i) Lei, B.-L.; Ding, C.-H.; Yang, X.-F.; Wan, X.-L.; Hou, X.-L. *J. Am. Chem. Soc.* **2009**, *131*, 18250.

(3) For special issues on organocatalysis, see: (a) *Acc. Chem. Res.* 2004, *37*, issue 8. (b) *Adv. Synth. Catal.* 2004, *346*, issues 9−10. (c) Berkessel, A.; Grçger, H. *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*; Wiley-VCH: Weinheim, 2005. (d) *Chem. Rev.* 2007, *107*, issue 12. (e) Dalko, P. I. *Enantioselective Organoctalysis*; Wiley-VCH: Weinheim, 2007. For a recent review on organocatalysis, see: (f) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703.

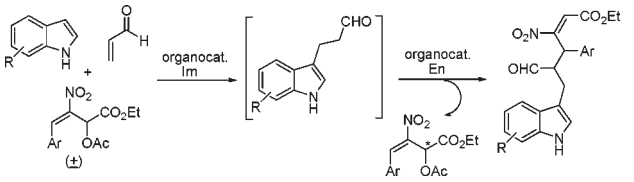
(4) (a) Berkessel, A.; Cleemann, F.; Mukherjee, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 7466. (b) Chen, L.; Luo, S.; Li, J.; Li, X.; Cheng, J.-P. *Org. Biomol. Chem.* **2010**, *8*, 2627. (c) Yu, J.; Chen, W.-J.; Gong, L.-Z. *Org. Lett.* **2010**, *12*, 4050. (d) Xie, J.-W.; Fan, L.-P.; Su, H.; Li, X.-S.; Xu, D.-C. *Org. Biomol. Chem.* **2010**, *8*, 2117. (e) For the first example of organocascade kinetic resolution, see: McGarraugh, P. G.; Brenner-Moyer, S. E. *Org. Lett.* **2011**, *13*, 6460.

10.1021/ol300783e
Published on Web 05/04/2012

been attained in a few isolated cases,[4] with numerous challenges and synthetic opportunities still remaining. Despite organocatalytic multicomponent cascade reactions[5] having been explored extensively in the literature, there exist only a handful of examples of this type of process ever being used in KR.[4e]

Recently, our research group reported a useful new organocatalytic kinetic resolution of racemic nitroallylic acetates that takes advantage of a novel conjugate addition-elimination S_N2' process.[6] Indole derivatives constitute a ubiquitous class of biologically active substance, and many such ring systems are found in important natural products and pharmaceuticals.[7] As such, there is substantial synthetic interest in the preparation of these substances, most especially indoles that possess chiral side chains or annulated chiral ring systems with side chains.[8] The Friedel–Crafts alkylation of indole with α,β-unsaturated carbonyls has been extensively explored for the construction of "privileged" indole frameworks.[9] We now present an efficient strategy for the three-component organocascade kinetic resolution involving indole, acrolein, and racemic nitroallylic acetates.

Scheme 1. Three-Component Organocascade Kinetic Resolution



The reaction proceeds through a sequential Friedel–Crafts-type/conjugate addition-elimination (S_N2') reaction initiated by a chiral iminium/enamine catalytic pathway. The resulting densely functionalized 3-alkylated indole derivatives are typically obtained in enantiomerically enriched form in good to excellent ee (83–99%), while the less reactive nitroallylic acetate enantiomers are also often recovered with high optical purity (79–95% ee).

In this study we have once more chosen indole and acrolein as reaction partners for a series of reactions mediated by the diphenylprolinol trimethylsilyl ether[5b,e,g,h,k,l,10] (**2**, 5 mol %), but on this occasion, we have also incorporated a third possible coupling component, namely, a racemic ethyl 2-acetoxy-3-nitro-4-arylbut-3(*E*)-enoate.[11] It was reasoned that the in situ generated 3-indoyl aldehyde would be a suitable intermediate for the kinetic resolution of a nitroallylic acetate via enamine catalysis (Scheme 1).

Our first attempt at performing this reaction using indole (0.3 mmol), acrolein (0.4 mmol), and the nitroallylic acetate **1a** (0.2 mmol) in toluene at ambient temperature failed (Table 1, entry 1). However, a lowering of the reaction temperature did prove beneficial and led to good results. Indeed, when we carried out the aforementioned reaction in CH_2Cl_2 at 0 °C, the highly 3-substituted indole derivative **3a** was isolated with excellent enantiomeric enrichment (98%) (Table 1, entry 2). The unreacted nitroallylic acetate was also recovered in reasonably good enantiomeric excess (81%) at 60% conversion. With this encouraging result in hand, we directed our attention toward optimizing the reaction conditions to maximize enantioselectivity for both product and unreacted substrate. As a result of solvent screening we quickly established that toluene was the best solvent for effecting this

(5) For reviews on organocatalytic cascade reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237. For selected examples of multicomponent organocatalytic cascade reactions, see: (c) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2003**, *42*, 4233. (d) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (e) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1101. (f) Jiang, J.; Yu, J.; Sun, X.-X.; Rao, Q.-Q.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2008**, *47*, 2458. (g) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem.—Eur. J.* **2008**, *14*, 4788. (h) Evans, C. G.; Gestwicki, J. E. *Org. Lett.* **2009**, *11*, 2957. (i) Zhang, F.-L.; Xu, A.-W.; Gong, Y.-F.; Wei, M.-H.; Yang, X.-L. *Chem.—Eur. J.* **2009**, *15*, 6815. (j) Enders, D.; Jeanty, M.; Bats, J. W. *Synlett* **2009**, 3175. (k) Chen, X.-H.; Wei, Q.; Luo, S.-W.; Xiao, H.; Gong, L.-Z. *J. Am. Chem. Soc.* **2009**, *131*, 13819. (l) Wang, Y.; Han, R.-G.; Zhao, Y.-L.; Yang, S.; Xu, P.-F.; Dixon, D. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9834. (m) García Ruano, J. L.; Marcos, V.; Suanzes, J. A.; Marzo, L.; Alemán, J. *Chem.—Eur. J.* **2009**, *15*, 6576. (n) Bencivenni, G.; Wu, L. Y.; Mazzanti, A.; Giannichi, B.; Pesciaioli, F.; Song, M.-P.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7200. (o) Chen, W.-B.; Wu, Z.-J.; Pei, Q.-L.; Cun, L.-F.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2010**, *12*, 3132. (p) Wang, Y.; Yu, D.-F.; Liu, Y.-Z.; Wei, H.; Luo, Y.-C.; Dixon, D. J.; Xu, P.-F. *Chem.—Eur. J.* **2010**, *16*, 3922. (q) Jensen, K. L.; Dickmeiss, G.; Donslund, B. S.; Poulsen, P. H.; Jørgensen, K. A. *Org. Lett.* **2011**, *13*, 3678. (r) Hong, B.-C.; Dange, N. S.; Hsu, C.-S.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2011**, *13*, 1338. (s) Ishikawa, H.; Sawano, S.; Yasui, Y.; Shibata, Y.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 3774.

(6) (a) Reddy, R. J.; Chen, K. *Org. Lett.* **2011**, *13*, 1458. (b) Reddy, R. J.; Lee, P.-H.; Magar, D. R.; Chen, J.-H.; Chen, K. *Eur. J. Org. Chem.* **2012**, 353.

(7) (a) Lounasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (c) O'Connor, S. E.; Maresh, J. J. *Nat. Prod. Rep.* **2006**, *23*, 532. (d) Kochanowska-Karamyan, A.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489.

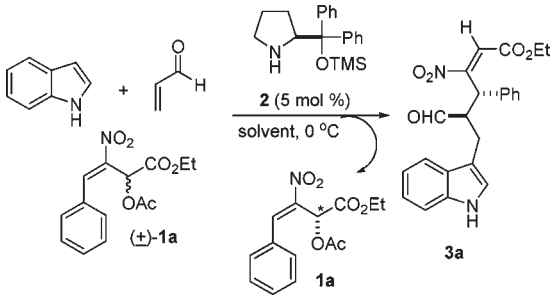
(8) (a) Jensen, K. B.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *Angew Chem., Int. Ed.* **2001**, *40*, 160. (b) Shiri, M.; Zolfigol, M. A.; Ayazi-Nasrabadi, R. *Tetrahedron Lett.* **2010**, *51*, 264. (c) García-Rubia, A.; Urones, B.; Arrayás, R. G.; Carretero, J. C. *Chem.—Eur. J.* **2010**, *16*, 9676. (d) Rajabi, F.; Razavi, S.; Luque, R. *Green Chem.* **2010**, *12*, 786.

(9) For a recent review, see: (a) Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. For organocatalytic indole Friedel–Crafts reactions, see: (b) Austin, J. F.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 1172. (c) King, H. D.; Meng, Z.; Denhart, D.; Mattson, R.; Kimura, R.; Wu, D.; Gao, Q.; Macor, J. E. *Org. Lett.* **2005**, *7*, 3437. (d) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (e) Galzerano, P.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2009**, *48*, 7892. (f) Hong, L.; Wang, L.; Chen, C.; Zhang, B.; Wang, R. *Adv. Synth. Catal.* **2009**, *351*, 772. (g) Enders, D.; Wang, C.; Mukanova, M.; Greb, A. *Chem. Commun.* **2010**, *46*, 2447.

(10) For recent reviews on diarylprolinolsilyl ether, see: (a) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922. (b) Xu, L.-W.; Li, L.; Shi, Z.-H. *Adv. Synth. Catal.* **2010**, *352*, 243. (c) Jensen, K. L.; Dickmeiss, G.; Jiang, H.; Albrecht, Ł.; Jørgensen, K. A. *Acc. Chem. Res.* **2012**, *45*, 248. For some recent references for diphenylprolinol trimethylsilyl ether **2** catalyzed reaction, see: (d) Belot, S.; Vogt, K. A.; Besnard, C.; Krause, N.; Alexakis, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 8923. (e) Companyo, X.; Zea, A.; Alba, A.-N. R.; Mazzanti, A.; Moyano, A.; Rios, R. *Chem. Commun.* **2010**, *46*, 6953. (f) Zhu, S.; Yu, S.; Wang, Y.; Ma, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 4656. (g) Anwar, S.; Chang, H.-J.; Chen, K. *Org. Lett.* **2011**, *13*, 2200. (h) Chen, J.-H.; Chang, C.; Chang, H.-J.; Chen, K. *Org. Biomol. Chem.* **2011**, *9*, 7510. (i) Cao, Y.-J.; Cheng, H.-G.; Lu, L.-Q.; Zhang, J.-J.; Cheng, Y.; Chen, J.-R.; Xiao, W.-J. *Adv. Synth. Catal.* **2011**, *353*, 617.

(11) Kuan, H.-H.; Reddy, R. J.; Chen, K. *Tetrahedron* **2010**, *66*, 9875.

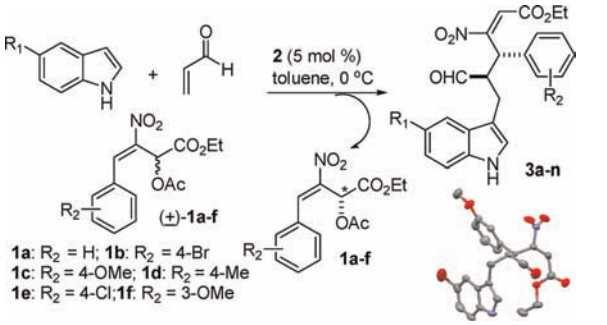
Table 1. Optimization of Three-Component Organocascade Kinetic Resolution[a]



entry	solvent	time (h)	conv (%)[b]	**3a** yield (%)[b]	**3a** ee (%)[c,d]	**1a** ee (%)[c]
1[e]	toluene					
2	CH_2Cl_2	7	60	41	98	81
3	THF	36	13	10		
4	CH_3CO_2Et	13	51	34	98	77
5	hexanes	6	46	23	98	49
6	toluene	6.5	58	49	98	91
7	EtOH	24	<5			
8	CH_3CN	48	24	13		
9	$CHCl_3$	7	61	38	98	83
10	Et_2O	9	63	35	99	91
11[f]	toluene	6	57	41	98	91
12[g]	toluene	6.5	61	42	98	86
13[h]	toluene	7	62	44	98	91
14[i]	toluene	6	69	40	98	92
15[j]	toluene	12	54	35	98	77

[a] Unless otherwise mentioned, all reactions were carried out with indole (0.3 mmol), acrolein (0.4 mmol), and nitroallylic acetate **1a** (0.2 mmol) in the presence of organocatalysts **2** (5 mol %) in indicated solvent (0.2 mL) at 0 °C. [b] Conversion and yield of **3a** were determined by ^{1}H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [c] Ee was determined by chiral HPLC analysis. [d] Dr (>99:1) of **3a** was determined by ^{1}H NMR analysis of crude reaction mixture. [e] Reaction was performed at 25 °C. [f] $PhCO_2H$ (10 mol %). [g] 2-$FPhCO_2H$ (10 mol %). [h] AcOH (15 mol %) was used as additive. [i] Catalyst **2** (10 mol %) was used with 0.5 M reaction concentration. [j] Catalyst **2** (2.5 mol %) was used.

Table 2. Substrate Scopes of the Organocascade Kinetic Resolution[a]



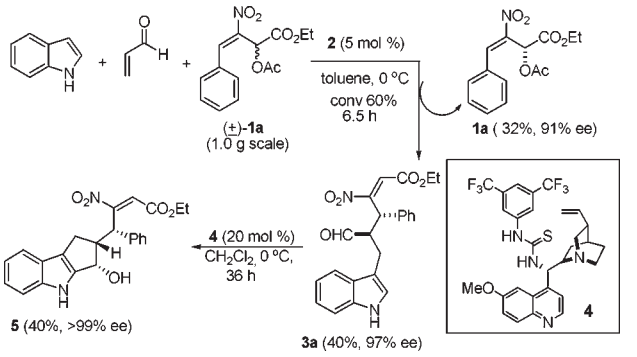
entry	R_1	**1**	time (h)	conv (%)[b]	yield **3** (%)[c]	yield **1** (%)[c]	ee (%)[d] **3**/**1**
1	H	**1a**	6.5	58	**3a**/47	**1a**/36	98/91
2	H	**1b**	5.5	60	**3b**/45	**1b**/36	96/91
3	H	**1c**	6.5	61	**3c**/30	**1c**/31	98/82
4	H	**1d**	6	55	**3d**/35	**1d**/39	98/84
5	H	**1e**	6.5	65	**3e**/38	**1e**/31	95/88
6	Br	**1b**	4	66	**3f**/35	**1b**/30	87/85
7	Br	**1d**	6.5	64	**3g**/43	**1d**/30	86/95
8	Br	**1f**	5	68	**3h**/29	**1f**/24	99/89
9	Cl	**1a**	6	63	**3i**/35	**1a**/30	99/90
10	Cl	**1e**	6	66	**3j**/37	**1e**/30	83/87
11	Cl	**1b**	4.5	61	**3k**/34	**1b**/36	90/81
12	Me	**1a**	6	59	**3l**/40	**1a**/36	97/86
13	Me	**1e**	6	65	**3m**/32	**1e**/30	90/86
14	OMe	**1a**	6.5	53	**3n**/33	**1a**/44	97/79
15[e]	H	**1a**	6.5	62	**3a**/36	**1a**/31	93/88[f]

[a] All reactions were carried out with indole (0.3 mmol), acrolein (0.4 mmol), and nitroallylic acetate **1a** (0.2 mmol) in the presence of orgaocatalysts **2** (5 mol %) in toluene (0.2 mL) at 0 °C. [b] Conversion was determined by ^{1}H NMR analysis of crude reaction mixture using CH_2Br_2 as an internal standard. [c] Isolated yield. [d] Ee was determined by chiral HPLC analysis. Diastereomeric ratios (>99:1) of products **3a**–**n** were determined by ^{1}H NMR analysis of crude reaction mixture. [e] Reaction was performed with (*R*)-**2** as a catalyst. [f] Opposite isomers.

reaction, both with respect to enantioselectivity and yield of product (Table 1, entry 6). We also screened different acid additives with a view to further improving our process but found that their presence was not especially advantageous; enantioselectivities remained the same or, in some case, actually diminished (Table 1, entries 11–13). Finally, we examined high and low catalyst loadings for our organocascade reaction and noticed that the use of 5 mol % **2** was optimal (Table 1, entries 14 and 15).

With finely tuned reaction conditions delineated, we next tried to demonstrate the generality of our new multicomponent KR process (Table 2). Nitroallylic acetates with different substitution patterns on the aryl group fell well within the remit of our process. 5-Substituted indoles also performed admirably. Extensive study further revealed that the reaction was slightly faster for the 4-bromo substituted nitroallylic acetate **1b**, and that this substrate also offered very good to moderate optically enriched products and unreacted substrate with different indoles (Table 2, entries 2, 6, and 11). Unsubstituted indoles also consistently afforded products with high enantioselectivity compared with their substituted analogues (Table 2, entries 1–5), while 5-bromo- and 5-chloroindoles afforded products with excellent enantioselectivity (99%) when combined with **1f** and **1a**, respectively (Table 2, entries 8 and 9). The 4-methyl substituted nitroallylic acetate (**1d**) only afforded the unreacted substrate with very high enantioselectivity (95%), when paired with 5-bromo indole (Table 2, entry 7). Indoles with electron-releasing groups generally impart high enantioselectivities to the products but also result in moderate enantioselectivities for the unreacted acetates (Table 2, entries 12–14). We have also carried out this KR process with (*R*)-diphenylprolinol trimethylsilyl ether (*ent*-**2**), under the optimized reaction conditions, and obtained product and unreacted acetate of comparable enantioselectivity and opposite configuration to those obtained with the (*S*)-catalyst (Table 2, entries 1 and 15).

Scheme 2. Synthesis of Tetrahydrocyclopenta[*b*]indole Derivative **5**



We further examined the reproducibility of our KR process on gram scale and found that it performs similarly with regard to chemical yields and enantioselectivity (Scheme 2). The utility of the product **3a** was demonstrated by an intramolecular electrophilic cyclization reaction, using the quinine-based thiourea catalyst **4**, to obtain tetrahydrocyclopenta[*b*]indole derivative **5** with excellent enantiocontrol (> 99% ee).

It is worth mentioning that the KR process of various nitroallylic acetates **1a**–**f** via our three-component reaction with indoles and acrolein has provided good to excellent (up to > 99%) enantioselectivity for various products, alongside superb chemical yields and very high enantiomeric purity (up to 95%) for the unreacted substrates. The absolute configuration of the product **3h** was determined as (4*S*,5*R*) by single crystal X-ray data analysis,[12] while the unreacted substrates (*R*)-**1a**–**f** had their configurations determined by comparison with our previous report.[6b]

In conclusion, an interesting multicomponent organocascade kinetic resolution using indole, acrolein, and racemic nitroallylic acetates has been demonstrated. Low catalyst loading (5 mol %) of the organocatalyst was found to be enough for smooth progression of the KR process in a short time frame (4–7 h). The enantio-enriched, 3-alkylated indoles were obtained with high-to-excellent stereoselectivity, while the less reactive starting substrates could also be recovered with high optical purity. The reaction proceeds via a Friedel–Crafts/S_N2' addition–elimination process following sequential iminium/enamine catalysis. *This is the first example of a three-component coupling reaction being used to carry out an asymmetric kinetic resolution, and it has provided new insights and conceptual paradigms for novel organocascade kinetic resolution.* Further studies are underway.

Acknowledgment. We thank the National Science Council of the Republic of China (NSC 99-2113-M-003-002-MY3 and NSC 99-2119-M-003-001-MY2) and National Taiwan Normal University (99-D and 100-D-06) for financial support of this work. Our gratitude extends to the Academic Paper Editing Clinic at NTNU.

Supporting Information Available. Experimental procedures, characterization data for new compounds, and X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) The *trans* geometry of the double bond in **3a** was well-understood by the ^{1}H NMR analysis showing single proton signal as doublet at δ 6.96 with J = 2.0 Hz, due to the allylic coupling, see ref 6. Detailed X-ray crystallographic data for compound **3h** (CCDC 869206) is available from the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (www.ccdc.cam.ac. uk/data_request/cif).

The authors declare no competing financial interest.