Parallel Recognition by Kinetic Control with Imino Aldehyde Substrates that are Prone to Redistribution

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Abstract: One-shot treatment of a mixture of Danishefsky diene **4** and tetraallyltin **8** with 3-formylbenzylidene imines **1** in the presence of $Sc(OTf)_3$ catalyst provides a single product **13** as a result of exclusive Diels–Alder and allylation reactions on the imine and aldehyde functions, respectively. The chemoselectivities of the respective elementary reactions are improved in the parallel reaction, and the redistribution of substrate **1** that is induced readily by $Sc(OTf)_3$ is completely suppressed, thus offering a novel protocol for simplification of the multi-step chemical process.

Keywords: aldehydes; allylation; cycloaddition; Lewis acids; synthetic method

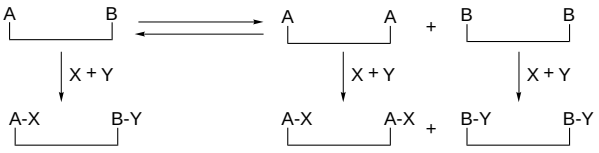
Introduction

Previously, we put forth a new concept for compaction of multi-step chemical processes, "parallel recognition".[1] Namely, two different reactions proceed simultaneously on separate reaction sites within a single molecule [Equation (1)]. Thus, both transformations of A to A-X

(1)

and of B to B-Y are feasible directly without protection of the A or B function so that the chemical process could enjoy improvement in conciseness and expedition. Besides such advantages in terms of process chemistry, if one takes account of a well-established concept, parallel kinetic resolution,[2] an improvement of chemoselectivity is expected because of the similarity between these two treatments.[3] One of the purposes of this paper is to demonstrate that this is indeed the case.

In the preceding examples, we always employed substrates that suffered no redistribution during the reaction. However, the situation is more complicated when the substrates are prone to scrambling as shown in Scheme 1. In this case, the desired product is contaminated by other products derived from the symmetrically proportioned components even if the two functions, A and B, preserve the specificity to X and Y, respectively. The second purpose is to demonstrate that the unique kinetic control in the parallel reaction enables a perfect recognition even for the substrates that are liable to such redistribution.



Scheme 1. Parallel reaction of a substrate undergoing redistribution.

Results and Discussion

Imino aldehydes **1** are the substrates of our choice on account of the biased reactivities of the two functions towards nucleophiles under catalysis by $Sc(OTf)_3$ (*vide infra*). On the basis of ^1H NMR spectra as shown in Scheme 2, it turned out that **1a** remained as a discrete species in CH_3CN or CH_2Cl_2 solution at 0 °C after 12 h while the facile scrambling to the symmetrical diimine **2a** and dialdehyde **3** occurred upon mixing with 10 mol % of $Sc(OTf)_3$ in the same solvent at 0 °C.

When **1a** was treated with the Danishefsky diene **4** (1.3 equiv.) in the presence of $Sc(OTf)_3$ (10 mol %) in CH_3CN at 0 °C for 3 min [Equation (2)], the Diels–Alder (DA) type reaction took place[4] preferentially with the imine function to furnish **5a** in 83% yield as the main product together with the bis-adduct **6a** (3%) after aqueous work-up. In keeping with the propensity of **1a** towards the redistribution, the bis-DA adduct **7a** derived from **2a** was formed in 5% yield together with the dialdehyde **3** (4%).

On the other hand, treatment of **1a** with tetraallyltin (**8**) (1.2 equiv. = 0.3 mol per 1 mol of **1a**) under the same conditions led to preferential allylation of the aldehyde

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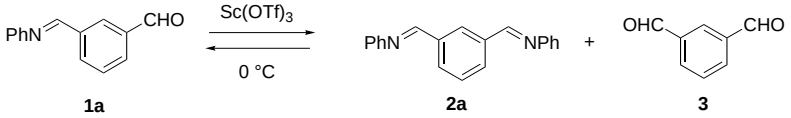
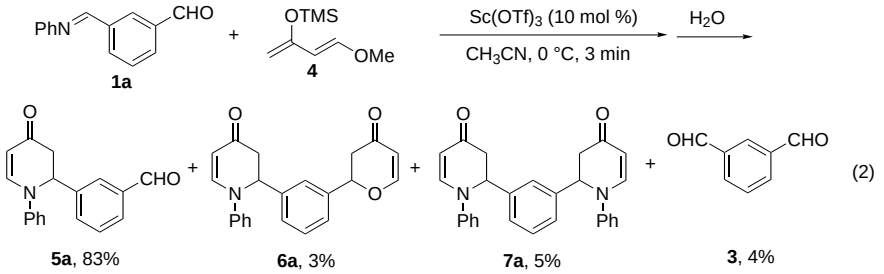


1a **2a** **3**

$Sc(OTf)_3$ [mol %]	Solvent	time [h]	**1a**:**2a**:**3a**
0	CH_3CN or CH_2Cl_2	12	100:0:0
10	CH_3CN	1	50:27:23
10	CH_2Cl_2	4	58:19:23

Scheme 2. Redistribution of an imino aldehyde on the basis of the ^{1}H NMR spectrum.



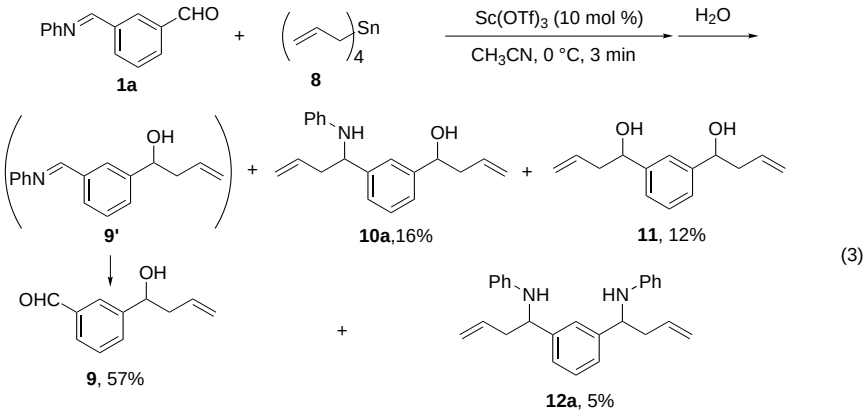
1a **4**

5a, 83% **6a**, 3% **7a**, 5% **3**, 4% (2)

function[5] to give **9** (57%) after hydrolysis of imine **9′** together with bis-allylation product **10a** (16%) [Equation (3)]. Notably, a greater degree of the redistribution was exercised in this case to afford **11** (12%) and **12a** (5%). In any event, the imine and aldehyde functions exhibited the opposite preference to **4** and **8** albeit with modest levels of selectivity.

In striking contrast to these results, when **1a** was treated with **4** (1.3 equiv.) and **8** (1.2 equiv.) simultaneously under the same conditions, **13a** was obtained as the sole product in quantitative yield, no other products being detected at all (Scheme 3). The benzylimine analogue **1b** gave rise to the similar outcome (**13b** in 91% yield).

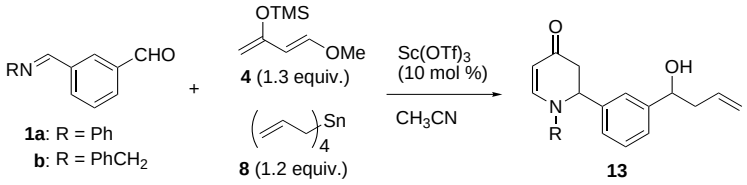
The imine reacted with **4** and the aldehyde with **8** in an exclusive manner: either the crossover reaction between the imine and **8** or that between the aldehyde and **4** was completely suppressed. In simple competition reactions like those in Equations (2) and (3), the product distribution reflects straightforwardly the relative reactivity of both functions towards the nucleophiles. By contrast, the parallel reaction virtually involves no such competition between these two functions. The slower reactions hardly occur since the imine or aldehyde function is more rapidly consumed by the faster reaction with the more reactive nucleophile and thus a set of the two faster reactions predominates on both functions. The perfect level of recognition, as attained above, would be accommodated in this kinetic notion. The concurrence of the two pathways (DA followed by allylation and allylation followed by DA) was confirmed by time-conversion analysis for the reaction of **1a** at –30 °C (Figure 1) where the intermediates **5a** and **9′** could be isolated as their *N,N*-dimethylhydrazone derivatives, **5a′** and **9″** [see Equations (4) and (5)].[6] The substrate **1a** disappeared very quickly (within 3 min). During this period, the amounts of the first DA and allylation intermediates were maximized and then gradually decreased. The mono-DA adduct **5a** was converted to **13a** completely after 1 h while the mono-allylation



1a **8**

9' **10a**,16% **11**, 12%

9, 57% **12a**, 5% (3)



1	Reaction temp. [C]	Reaction time [h]	Yield [%] of 13	
1a	0	2	**13a**	94
	-30	5		94
1b	0	10	**13b**	83
	-15	12		91

Scheme 3. Parallel recognition of imino aldehydes.

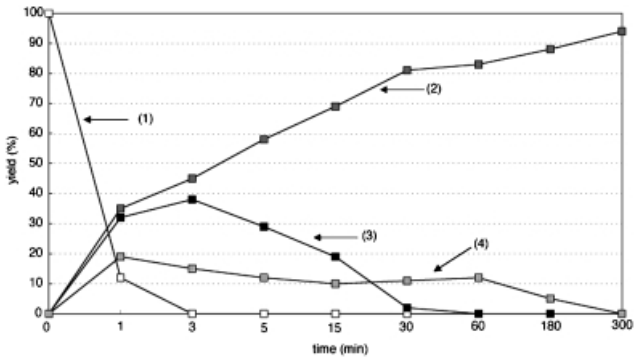
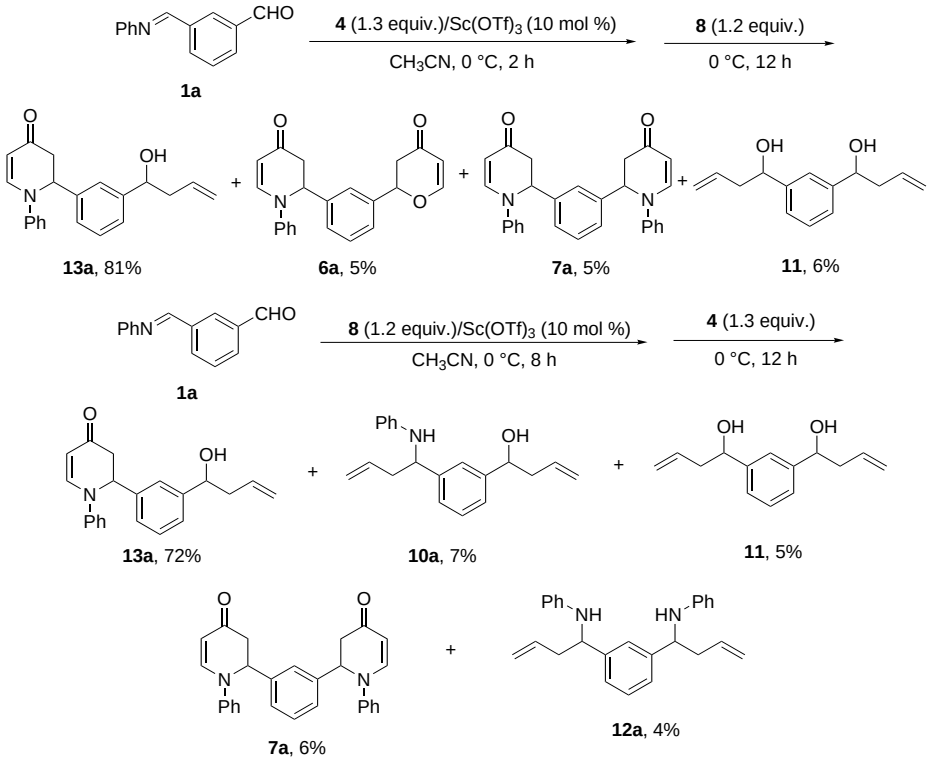


Figure 1. Time-conversion curve in the parallel reaction of **1a** with **4** and **8**: (1) **1a** as **14**; (2) **13a**; (3) **5** as **5a**′; and (4) **9**′ as **9**′′.

intermediate **9**′ was used up after 6 h when the overall reaction finished.

The complete suppression of the redistribution is another notable aspect. The characteristic features of the parallel recognition could be envisioned by comparison with the sequential reactions (Scheme 4). Exposure of **1a** to **4** for 2 h followed by **8** for 12 h under the same conditions as employed for the parallel reaction did not lead to the single product, instead four components constituted the product mixture. Apparently, less selective attack of **4** on the imine and aldehyde functions gave both **13a** and **6a** and the redistribution led to **7a** and **11**. The reversed addition of the nucleophiles (**8** followed by



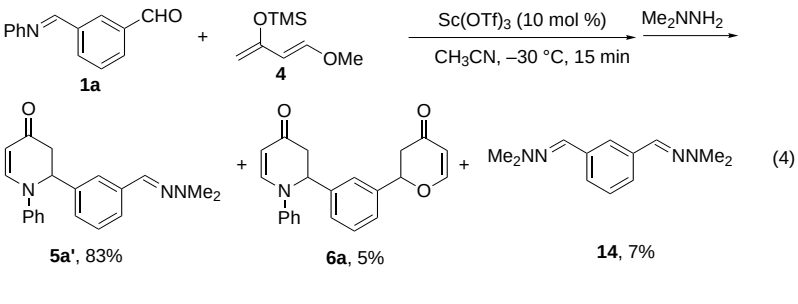
Scheme 4. Sequential reactions of **1a** with **4/8**.

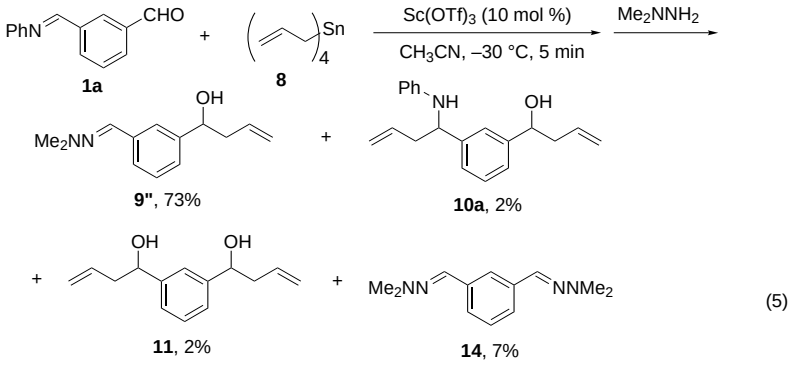
4) also exhibited a similar trend. In this case, bisallylation of the diimine also took place to give **12a**.

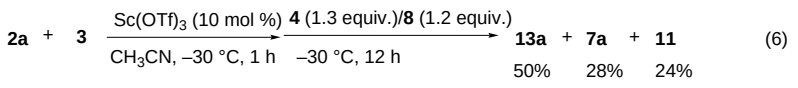
Then, the question was addressed why the parallel reaction gave rise to no redistribution. The answer is given on the basis of acceleration in the substrate consumption rate since the total concentration of the nucleophiles relative to the substrate is doubled under the parallel reaction conditions. As a consequence, the imino aldehyde substrate disappears at a much greater rate than that of the redistribution reaction. The reactions at –30 °C were examined to confirm this postulate because reactions at higher temperatures were too fast to perform a reliable analysis. When the reaction of **1a** with **4** (1.3 equiv.) was conducted at –30 °C, hydrazone **5a**′ was obtained in 83% yield together with 5% of **6a** through quenching with Me_2NNH_2 after 15 min [Equation (4)]. The total DA reaction yield (88%) is comparable to that in the parallel reaction which gave rise to an 88% total yield (69% of **13a** and 19% of **5a**′) (see Figure 1). It should be noted that, under parallel reaction conditions, another reagent **8** also can attack the substrate and probably the redistribution surrenders to the competing allylation. The same situation arose on treatment of **1a** with **8** to provide a 73% yield of **9**″ together with a 2% yield of **10a** after 5 min [Equation (5)], a total initial allylation yield (75%) comparable to that of the parallel reaction (70% consisting of 58% of **13a** and 12% of **9**″). Thus, the relief from the redistribution can be interpreted in terms of the increase in the total concentration of the reagents to consume the substrate more rapidly than scrambling under the parallel reaction conditions.

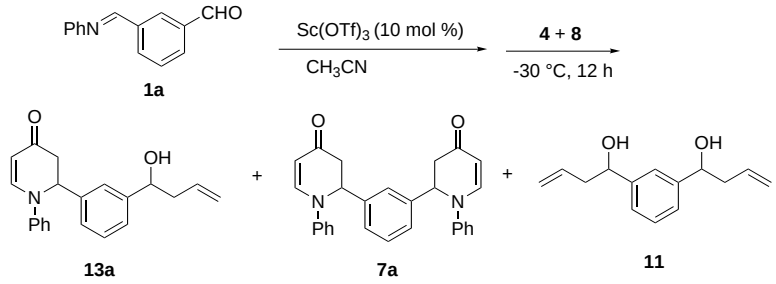
The absence of the redistribution in the parallel system gained further support from the subsequent events. A solution of **1a** and $Sc(OTf)_3$ (10 mol %) in CH_3CN was stirred for 3 min and then the mixture of **4** and **8** was added to this solution at –30 °C (Scheme 5). After 12 h, the redistribution products **7a** (3%) and **11** (4%) were obtained besides **13a** (89%), indicative of the redistribution in ca. 4% conversion after 3 min in the absence of the nucleophiles. When **1a** and $Sc(OTf)_3$ were stirred for 1 h prior to the treatment with the nucleophiles, the products distribution was nearly consistent with that expected from the thermodynamic equilibration. The same procedure at 0 °C gave similar results which revealed that *ca.* 9% redistribution was reached after 3 min. This stands in sharp contrast with the outcome given in Figure 1.

The thermodynamic product distribution was also attained by the reverse reaction [Equation (6)]. An equimolar mixture of diimine **2a** and dialdehyde **3** was stirred for 1 h. Addition of the mixture of **4** and **8** to this solution provided **13a**, **7a**, and **11** in a *ca.* 2:1:1 ratio. Finally, the reverse reaction provided conclusive evidence for the relief from the redistribution in the parallel system (Scheme 6). A mixture of **1a**, **2a**, and **3** was treated with the mixture of **4** and **8** at –30 °C. The product distribution (**13a**:**7a**:**11**) was totally reminiscent of the initial substrate ratio. Apparently, each substrate was used up before the redistribution.



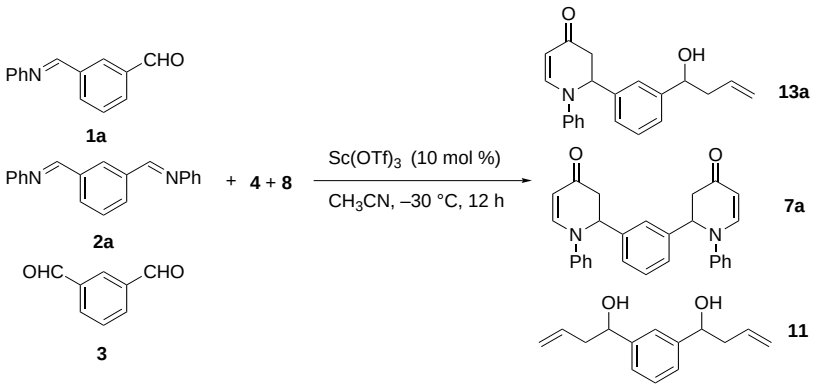






Conditions for mixing of **1a** with $Sc(OTf)_3$	Yield [%]		
	13a	**7a**	**11**
-30 °C, 3 min	89	3	4
-30 °C, 1 h	51	28	26
0 °C, 3 min	85	7	9
0 °C, 1 h	51	28	26

Scheme 5. Initial treatment of **1a** with $Sc(OTf)_3$ followed by the mixture of **4** and **8**.



1a:**2a**:**3**	Yield [%]		
	13a	**7a**	**11**
0:1:1	0	97	89
1:5:5	100	485 (97 x 5)	445 (91 x 5)

Scheme 6. Parallel recognition of mixed substrates.

Conclusion

In conclusion, the selectivity of the imine function towards the Danishefsky diene as well as of the aldehyde function toward tetraallyltin is enhanced to effect perfect recognition in the parallel reaction. The rapid consumption of the substrates relieves the reaction from the redistribution. These results not only increase the synthetic promise of "parallel recognition" but also raise a novel and fundamental mechanistic view that the parallel reaction is not the simple superimposition of the elementary reactions.

Experimental Section

General Remarks

All reactions were carried out under an atmosphere of nitrogen with freshly distilled solvents, unless otherwise noted. Acetonitrile was distilled from CaH_2. Benzene was distilled from sodium. Danishefsky diene and tetraallyltin were purchased and used without purification. Silica gel (Daiso gel IR-60) was used for column chromatography. NMR spectra were recorded at 25 °C on Varian Gemini-300, JEOL Lambda 300, and JEOL Lambda 500 instruments and calibrated with tetramethylsilane (TMS) as an internal reference. Mass spectra were recorded on a Jeol MStation JMS-700 spectrometer, Shimadzu/Kratos MALDI 4, and Platform II single quadrupole mass spectrometer (Micromass, Altrinchan, UK).

Preparation of 1

To isophthalaldehyde (1.34 g, 10.0 mmol) in benzene (10 mL) was added aniline (0.91 mL, 10 mmol) dropwise by a syringe at room temperature, and the mixture was stirred for 10 h. After addition of Na_2SO_4, the mixture was filtered, and the filtrate was evaporated. The residual oil was subjected to Kugelrohr distillation (200 °C/1.0 mm Hg) to give **1a** in pure form; yield: 669mg (32%). ^{1}H NMR ($CDCl_3$): δ = 7.22 – 7.29 (m, 3H), 7.39 – 7.45 (m, 2H), 7.67 (t, *J* = 7.7 Hz, 1H), 8.00 (d, *J* = 1.5 Hz, 1H), 8.20 (d, *J* = 1.5 Hz, 1H), 8.41 (s, 1H), 8.55 (s, 1H), 10.1 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 120.8, 126.4, 129.2, 129.4, 130.1, 131.6, 134.1, 136.8, 137.1, 151.3, 158.5, 191.7; HRMS (EI): calcd. for $C_{14}H_{11}ON$: 209.0841; found: 209.0849.

Compound **1b** was prepared analogously by the reaction of **3** with benzylamine. ^{1}H NMR ($CDCl_3$): δ = 4.85 (s, 2H), 7.25 – 7.36 (m, 5H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.6 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 8.26 (s, 1H), 8.44 (s, 1H), 10.00 (s, 1H). ^{13}C NMR ($CDCl_3$): δ = 64.9, 127.1, 127.9, 128.5, 129.3, 129.7131.1, 133.7, 136.7, 137.0, 138.7, 160.3, 191.8; HRMS (EI): calcd. for $C_{15}H_{13}ON$: 223.0997; found: 223.0993.

Redistribution of 1a (Scheme 2)

To a round-bottomed flask were added **1a** (105 mg, 0.5 mmol), CD_3CN (3 mL), and $Sc(OTf)_3$ (25 mg, 0.05 mmol) at 0 °C, and the mixture was stirred for 1 h. The mixture was transferred to an NMR sample tube, and ^{1}H NMR spectrum was measured to reveal that the mixture was composed of **1a** (50%), **2a** (27%) and **3** (23%).

2a: ^{1}H NMR ($CDCl_3$): δ = 7.23 – 7.27 (m, 6H), 7.40 – 7.43 (m, 4H), 7.60 (t, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 7.6 Hz, 1H), 8.05 (d, *J* = 7.6 Hz, 1H), 8.41 (s, 1H), 8.54 (s, 2H); ^{13}C NMR ($CDCl_3$): δ = 120.9, 126.2, 129.2, 129.24, 129.3, 131.2, 136.8, 151.7, 159.5; HRMS (EI): calcd. for $C_{20}H_{16}N_2$: 284.1313; found: 284.1321.

Diels–Alder Reaction between 1a and 4 [Eq. (2)]

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (105 mg, 0.5 mmol) and **4** (0.13 mL, 0.65 mmol) in CH_3CN (1 mL) at 0 °C. The mixture was stirred for 3 min. Water (5 mL) was added, and the mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4 and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using a gradient solvent system to afford **3** (10:90 AcOEt/hexane); yield: 3 mg (4%); **5a** (50:50 AcOEt/hexane); yield: 115 mg (83%); **6a** (60:40 AcOEt/hexane); yield: 5 mg (3%); and **7a** (80:20 AcOEt/hexane); yield: 11 mg (5%).

5a: ^{1}H NMR ($CDCl_3$): δ = 2.80 and 3.35 (ABX, J_{AB} = 16.4 Hz, J_{AX} = 7.1 Hz, J_{BX} = 3.9 Hz, 2H), 5.31 – 5.39 (m, 2H), 6.99 – 7.02 (m, 2H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.26 – 7.29 (m, 2H), 7.51 – 7.59 (m, 2H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.79 – 7.82 (m, 2H), 10.0 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 42.9, 60.9, 103.0, 118.2, 124.4, 126.7, 129.5, 129.6, 132.0, 136.7, 139.1, 144.1, 148.0, 189.4, 191.6; HRMS (EI): calcd. for $C_{18}H_{15}O_2N$: 277.1103; found: 277.1104.

6a: ^{1}H NMR ($CDCl_3$): δ = 2.59 – 2.64 (m, 1H), 2.76 – 2.87 (m, 2H), 3.33 (m, 1H), 5.29 – 5.32 (m, 2H), 5.39 (dd, *J* = 3.2, 14.4 Hz, 1H), 5.51 (d, *J* = 6.2 Hz, 1H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.13 (t, *J* = 7.2 Hz, 1H), 7.29 – 7.46 (m, 7H), 7.68 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$): (major) δ = 43.0, 61.3, 80.4, 102.8, 107.2, 118.4, 123.6, 124.4, 125.3, 126.4, 128.1, 129.3, 129.8, 138.6, 144.3, 148.1, 162.8, 189.8, 191.6; (minor) δ = 43.0, 61.3, 80.4, 102.7, 107.2, 118.4, 123.6, 124.4, 125.3, 126.4, 128.1, 129.3, 129.8, 138.6, 144.3, 148.2, 162.9, 189.8, 191.6; HRMS (EI): calcd. for $C_{22}H_{19}O_3N$: 345.1364; found: 345.1361.

7a: ^{1}H NMR ($CDCl_3$): δ = 2.61 (dd, *J* = 3.4, 16.5 Hz, 1H), 2.67 (dd, *J* = 3.2, 16.6 Hz, 1H), 3.10 – 3.18 (m, 2H), 5.09 (d, *J* = 7.9 Hz, 1H), 5.12 – 5.18 (m, 3H), 6.84 – 7.30 (m, 4H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.50 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): (major) δ = 42.9, 61.2, 102.6, 118.7, 124.2, 124.5, 125.7, 138.4, 144.2, 148.2, 189.5; (minor) δ = 43.1, 61.3, 102.5, 118.8, 124.0, 124.5, 125.8, 138.7, 144.2, 148.5, 189.5; HRMS (EI): calcd. for $C_{28}H_{24}O_2N_2$: 420.1838; found: 420.1836.

Allylation of 1a with 8 [Eq. (3)]

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (105 mg, 0.5 mmol) and **8** (0.04 mL, 0.15 mmol) in CH_3CN (1 mL) at 0 °C. The mixture was stirred for 3 min. Water (5 mL) was added, and the mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4 and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using a gradient solvent system to afford **12a** (5:95 AcOEt/hexane); yield: 9 mg (5%); **10a** (10:90 AcOEt/hexane); yield: 23 mg (16%); **9** (20:80 AcOEt/hexane); yield: 50 mg (57%); and **11** (30:70 AcOEt/hexane); yield: 13 mg (12%).

9: ^{1}H NMR ($CDCl_3$): δ = 2.19 (br, 1H), 2.44 – 2.63 (m, 2H), 4.85 (br, 1H), 5.20 (d, *J* = 1.1 Hz, 1H), 5.22 (d, *J* = 1.3 Hz, 1H), 5.71 – 5.88 (m, 1H), 7.53 (t, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 7.7 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.90 (s, 1H), 10.0 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 43.8, 72.5, 118.9, 126.9, 128.9, 129.0, 131.9, 133.7, 136.4, 145.0, 192.4; HRMS (EI): calcd. for $C_{11}H_{11}O_2$: 175.0759; found: 175.0742.

10a: ^{1}H NMR ($CDCl_3$): δ = 2.04 (br, 1H), 2.56 (m, 4H), 4.16 (br, 1H), 4.38 (dd, *J* = 5.4, 7.8 Hz, 1H), 4.73 (br, 1H), 5.15 (m, 1H), 5.76 (m, 2H), 6.48 (d, *J* = 7.8 Hz, 2H), 6.64 (t, *J* = 7.3 Hz, 1H), 7.06 (m, 2H), 7.22 – 7.34 (m, 4H); ^{13}C NMR ($CDCl_3$): (major) δ = 43.2, 43.7, 57.2, 73.2, 113.5, 117.3, 118.1, 118.2, 123.6, 124.4, 125.4, 128.6, 128.9, 134.3, 134.5, 143.7, 144.1, 147.2; (minor) δ = 43.2, 43.7, 57.2, 73.2, 113.5, 117.3, 118.1, 118.2, 123.7, 124.4, 125.4, 128.6, 128.9, 134.3, 134.5, 143.7, 144.1, 147.2; HRMS (EI): calcd. for $C_{20}H_{23}ON$: 293.1780; found: 293.1784.

11: ^{1}H NMR ($CDCl_3$): δ = 2.04 (br, 2H), 2.44 – 2.59 (m, 4H), 4.75 (dd, *J* = 5.2, 7.6 Hz, 2H), 5.14 – 5.20 (m, 4H), 5.75 – 5.89 (m,2H), 7.26 – 7.37 (m, 4H); ^{13}C NMR ($CDCl_3$): δ = 43.7, 73.2, 73.3, 118.3, 123.2, 123.3, 124.9, 125.0, 128.4, 128.5, 134.4, 144.0, 144.1; HRMS (EI): calcd. for $C_{14}H_{18}O_2$: 218.1306; found: 218.1319.

12a: ^{1}H NMR ($CDCl_3$): δ = 2.41 – 2.59 (m, 4H), 4.11 (br, 2H), 4.32 – 4.37 (m, 2H), 5.07 – 5.15 (m, 4H), 5.62 – 5.76 (m, 2H), 6.42 – 6.48 (m, 4H), 6.61 – 6.65 (m, 2H), 7.02 – 7.08 (m, 4H), 7.31 – 7.69 (m, 4H); ^{13}C NMR ($CDCl_3$): (major) δ = 43.2, 57.2, 113.6, 117.3, 118.2, 124.7, 125.0, 128.9, 129.0, 134.6, 143.7, 147.3; (minor) δ = 43.1, 57.3, 113.6, 117.4, 118.3, 124.5, 124.8, 128.9,

129.0, 134.5, 143.7, 147.3; HRMS (EI): calcd. for $C_{26}H_{28}N_2$: 368.2252; found: 368.2266.

Parallel Reaction of 1a with 4 and 8 (Scheme 3)

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (105 mg, 0.5 mmol), **4** (0.13 mL, 0.65 mmol), and **8** (0.04 mL, 0.15 mmol) in CH_3CN (1 mL) at 0 °C. The mixture was stirred for 2 h. Water (5 mL) was added, and the mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4 and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel (60:40 AcOEt/hexane) to afford pure **13a**; yield: 150 mg (94%), as a 53:47 mixture of diastereomers. ^{1}H NMR ($CDCl_3$): δ = 2.04 (br, 1H), 2.43 – 2.47 (m, 2H), 2.79 (d, J = 16.7 Hz, 1H), 3.30 (dd, J = 7.2, 16.3 Hz, 1H), 4.70 (t, J = 6.3 Hz, 1H), 5.10 – 5.15 (m, 2H), 5.27 (d, J = 7.5 Hz, 2H), 7.00 – 7.32 (m, 9H), 7.66 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$): δ = 43.1 (minor), 43.2, 43.5 (minor), 43.6, 61.45, 61.49 (minor), 72.7, 72.8 (minor), 102.3, 102.4 (minor), 117.77, 117.85 (minor), 118.5 (minor), 118.6, 123.4, 123.6, 124.28 (minor), 124.31, 124.82 (minor), 124.84, 125.2, 125.3 (minor), 128.65, 128.70 (minor), 134.17, 134.20 (minor), 137.7, 144.4, 145.0, 148.6, 190.3; HRMS (EI): calcd. for $C_{21}H_{21}O_2N$: 319.1572; found: 319.1567.

Compound **13b** (52:48 mixture of diastereomers) was obtained by the analogous treatment of **1b** with **4** and **8**. ^{1}H NMR ($CDCl_3$): δ = 2.14 (br, 1H), 2.44 – 2.49 (m, 2H), 2.69 and 2.83 (ABX, J_{AB} = 16.5 Hz, J_{AX} = 8.3 Hz, J_{BX} = 7.0 Hz, 2H), 4.12 and 4.35 (ABq, J = 15.2 Hz, 2H), 4.52 (t, J = 6.4 Hz, 1H), 5.08 – 5.17 (m, 3H), 5.74 – 5.83 (m, 1H), 7.09 – 7.38 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 43.31 (minor), 43.33, 43.66, 43.69 (minor), 57.0, 60.5, 72.7 (minor), 72.8, 98.2, 117.8, 124.47, 124.50 (minor), 125.7, 125.8, 127.5, 128.0, 128.68, 128.74, 134.3, 135.6, 138.17, 138.19 (minor), 145.13, 145.15 (minor), 154.5 190.4; HRMS (EI): calcd. for $C_{22}H_{23}O_2N$: 333.1729; found: 333.1722.

Time-Conversion Analysis (Representative, Figure 1)

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (105 mg, 0.5 mmol), **4** (0.13 mL, 0.65 mmol), and **8** (0.04 mL, 0.15 mmol) in CH_3CN (1 mL) at –30 °C. The mixture was stirred for 3 min. After addition of Me_2NNH_2 (0.08 mL, 1.0 mmol), the mixture was stirred for 10 min, and water (10 mL) was added. The mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, water, aqueous $NaHCO_3$, and brine. After drying over $MgSO_4$ and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel to afford **9″** (30:70 AcOEt/hexane); yield: 16 mg (15%) and a mixture of **13a** and **5a′** (60:40 AcOEt/hexane); yield: 133 mg. ^{1}H NMR analysis revealed that the mixture was composed of **13a** (72 mg, 45% yield) and **5a′** (61 mg, 38% yield).

5a′: ^{1}H NMR ($CDCl_3$): δ = 2.80 and 3.28 (ABX, J_{AB} = 16.3 Hz, J_{AX} = 7.2 Hz, J_{BX} = 2.6 Hz, 2H), 3.28 (dd, J=7.2 Hz, 16.3 Hz, 1H), 2.95 (s, 6H), 5.25 – 5.31 (m, 2H), 7.00 – 7.49 (m, 10H), 7.68 (d, J = 7.7 Hz, 1H); ^{13}C NMR($CDCl_3$): δ = 42.5, 61.4, 102.7, 118.2, 122.9, 124.1, 124.5, 124.9, 128.1, 128.8, 129.3, 131.5, 137.5, 138.0, 144.4, 148.0; HRMS (EI): calcd. for $C_{20}H_{21}ON_3$: 319.1685; found: 319.1689.

9″: ^{1}H NMR ($CDCl_3$): δ = 2.50 – 2.55 (m, 2H), 2.96 (s, 1H), 4.75 (t, J = 5.5 Hz, 1H), 5.13 – 5.20 (m, 2H), 5.76 – 5.89 (m, 1H), 7.21 – 7.33 (m, 3H), 7.46 (d, J = 7.5 Hz, 1H), 7.58 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 42.8, 43.6, 73.3, 118.1, 122.9, 124.7, 124.8, 128.5, 132.8, 134.5, 136.8, 144.2; HRMS (EI): calcd. for $C_{13}H_{18}ON_2$: 218.1419; found: 219.1429.

Sequential Reaction of 1a with 4 and 8 (Scheme 4)

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (105 mg, 0.5 mmol) and **4** (0.13 mL, 0.65 mmol) in CH_3CN (1 mL) at 0 °C. After the mixture had been stirred for 2 h, **8** (0.04 mL, 0.15 mmol) in CH_3CN (1 mL) was added, and the mixture was stirred for 12 h. Water (5 mL) was added, and the mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, aqueous $NaHCO_3$, and brine. After drying over Na_2SO_4 and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using gradient solvent system to afford **11** (30:70 AcOEt/hexane); yield: 7 mg (6%); **13a** (55:45 AcOEt/hexane); yield: 129 mg (81%); **6a** (60:40 AcOEt/hexane); yield: 9 mg (5%); and **7a** (80:20 AcOEt/hexane); yield: 11 mg (5%).

The sequential reaction of **1a** with **8** followed by **4** was carried out similarly to furnish **12a** (5:95 AcOEt/hexane); yield: 7 mg (4%); **10a** (10:90 AcOEt/hexane); yield: 10 mg (7%); **11** (30:70 AcOEt/hexane); yield: 5 mg (5%); **13a** (55:45 AcOEt/hexane); yield: 115 mg (72%); and **7a** (80:20 AcOEt/hexane); yield: 13 mg (6%).

Analysis of Product Distribution in Hetero-Diels–Alder Reaction by Quenching with Me_2NNH_2 [Eq.(4)]

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (105 mg, 0.5 mmol) and **4** (0.13 mL, 0.65 mmol) in CH_3CN (1 mL) at –30 °C. The mixture was stirred for 15 min. After addition of Me_2NNH_2 (0.08 mL, 1.0 mmol), the mixture was stirred for 10 min, and water (10 mL) was added. The mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, water, aqueous $NaHCO_3$, and brine. After drying over $MgSO_4$ and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using gradient solvent system to afford **5a′** (50:50 AcOEt/hexane); yield: 133 mg (83%); **6a** (60:40 AcOEt/hexane); yield: 9 mg (5%); and **14** (10:90 AcOEt/hexane); yield: 8 mg (7%).

14: ^{1}H NMR ($CDCl_3$): δ = 2.95 (s, 6H), 7.27 (t, J = 7.8 Hz, 1H), 7.35 (s, 1H), 7.44 and 7.45 (dd, J = 15.7, 7.6 Hz, 2H), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$): δ = 42.8, 123.1, 124.4, 128.6, 132.9, 136.9; HRMS (EI): calcd. for $C_{12}H_{18}N_4$: 218.1531; found: 218.1530.

Analysis of Products Distribution in Allylation by Quenching with Me_2NNH_2 [Eq. (5)]

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (105 mg, 0.5 mmol) and **8** (0.04 mL, 0.15 mmol) in CH_3CN (1 mL) at –30 °C. The mixture was stirred for 5 min. After addition of Me_2NNH_2 (0.08 mL, 1.0 mmol), the mixture was stirred for 10 min, and water (10 mL) was added. The mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, water, aqueous $NaHCO_3$, and brine. After drying over $MgSO_4$ and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using a gradient solvent system to afford **10a** (10:90 AcOEt/hexane); yield: 3 mg (2%); **14** (10:90 AcOEt/hexane); yield: 8 mg (10%); **9″** (25:75 AcOEt/hexane); yield: 80 mg (73%); and **11** (30:70 AcOEt/hexane); yield: 2 mg (2%).

Analysis of Product Distribution in Redistribution/Parallel Recognition Reaction [Eq. (6)]

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added a mixture of **2a** (71 mg, 0.25 mmol) and **3** (34 mg, 0.25 mmol) in CH_3CN (1 mL) at –30 °C. The mixture was stirred for 1 h. A mixture of **4** (0.13 mL, 0.65 mmol) and **8** (0.04 mL, 0.15 mmol) in CH_3CN (1 mL) was added at –30 °C. After the mixture had been stirred for 12 h, water (10 mL) was added, and the mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, water, aqueous $NaHCO_3$, and brine. After drying over $MgSO_4$ and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using a gradient solvent system to afford **11** (30:70 AcOEt/hexane; yield: 26 mg (24%); **13a** (55:45 AcOEt/hexane); yield: 80 mg (50%); and **7a** (80:20 AcOEt/hexane); yield: 59 mg (28%).

Parallel Recognition after Redistribution (Representative, Scheme 5)

To a solution of $Sc(OTf)_3$ (25 mg, 0.05 mmol) in CH_3CN (3 mL) was added **1a** (105 mg, 0.5 mmol) in CH_3CN (1 mL) at – 30 °C. The mixture was stirred for 1 h. A mixture of **4** (0.13 mL, 0.65 mmol) and **8** (0.04 mL, 0.15 mmol) in CH_3CN (1 mL) was added at –30 °C. After the mixture had been stirred for 12 h, water (10 mL) was added, and the mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, water, aqueous $NaHCO_3$, and brine. After drying over $MgSO_4$ and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using a gradient solvent system to afford **11** (30:70 AcOEt/hexane); yield: 28 mg (26%); **13a** (55:45 AcOEt/hexane); yield: 81 mg (51%); and **7a** (80:20 AcOEt/hexane); yield: 59 mg (28%).

Parallel Recognition of Mixed Substrates (Representative, Scheme 6)

To a solution of $Sc(OTf)_3$ (108 mg, 0.22 mmol) in CH_3CN (3 mL) was added a mixture of **1a** (42 mg, 0.2 mmol), **2a** (284 mg, 1.0 mmol), **3** (134 mg, 1.0 mmol), **4** (0.56 mL, 2.86 mmol), and **8** (0.16 mL, 0.66 mmol) in CH_3CN (1 mL) at –30 °C. After the mixture had been stirred for 12 h, water (10 mL) was added, and the mixture was extracted with water/AcOEt. The combined organic layer was washed with 1 N HCl, water, aqueous $NaHCO_3$, and brine. After drying over $MgSO_4$ and filtration, the organic layer was concentrated under reduced pressure. The crude mixture was subjected to column chromatography on silica gel by using a gradient solvent system to afford **11** (30:70 AcOEt/hexane); yield: 198 mg (445%, **13a** (60:40 AcOEt/hexane); yield: 64 mg (100%); and **7a** (80:20 AcOEt/hexane); yield: 408 mg (485%).

References and Notes

[1] a) J. Chen, J. Otera, *Angew. Chem*. **1998**, *110*, 96; *Angew. Chem. Int. Ed.* **1998**, *37*, 91; b) J. Chen. J. Otera, *Tetrahedron Lett*. **1998**, *39*, 1767; c) J. Chen, K. Sakamoto, A. Orita, J. Otera, *Tetrahedron* **1998**, *54*, 8411.

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[3] Mention was made in this relation by Vedejs et al. in their paper on parallel kinetic resolution as "In principle, mixtures of two achiral components (diastereomers; regioisomers; etc.) could also be derivatized with improved efficiency using two complementary reagents in parallel if they react selectively with each isomer to afford a distinct product": E. Vedejs, X. Chen, *J. Am. Chem. Soc*. **1997**, *119*, 2584.

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[5] I. Hachiya, S. Kobayashi, *J. Org. Chem*. **1993**, *58*, 6958.

[6] Aqueous quenching is not employable because the reaction of **8** with aldehydes proceeds in the presence of water.[5] We have found that addition of Me_2NNH_2 can quench the reaction instantaneously to allow the quantitative analysis. Note that addition of excess hydrazine induces conversion of the imine to the hydrazone, too.