DOI: 10.1002/ejoc.200800781

Chemospecific Allylation and Domino Metathesis of 7-Oxanorbornenes for Skeletal and Appendage Diversity

Minoru Ikoma,[a] Masato Oikawa,*[a] and Makoto Sasaki[a]

Keywords: Alkylation / Combinatorial chemistry / Domino reactions / Metathesis / Multicomponent reactions

We report a synthetic strategy for skeletally diverse heterocycles featuring appendage diversity based on a tandem Ugi/Diels–Alder reaction followed by domino metathesis. An associating effect of the amide carbonyl functionality to the ruthenium metal center is proposed in order to account for the difference in the metathesis yields.

Introduction

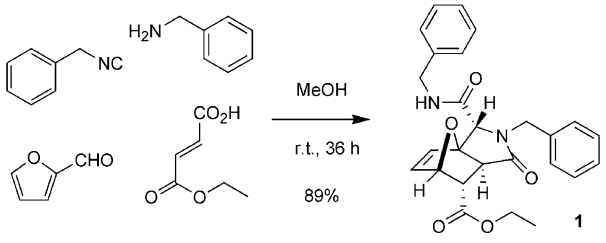
Metathesis plays a crucial role in modern synthetic organic chemistry. Olefin metathesis reactions are roughly categorized into three groups: cross metathesis (CM), ring-closing metathesis (RCM), and ring-opening metathesis (ROM). Since metathesis reactions provide complex molecular architectures not readily accessible by other organic transformations, they are now widely used even for the synthesis of biologically important, complex natural products.[1,2]

Domino metathesis sequences, in which two or more metathesis reactions take place sequentially, have also attracted considerable attention. In these studies, combinations of the above three types of metathesis reactions (CM, RCM, and ROM) have been extensively investigated.[3,4] In this regard, the norbornene skeleton is an interesting platform because it undergoes domino ROM/CM/RCM reactions to generate other complex skeletons.[5]

Combinations of these domino metathesis reactions with other multicomponent coupling reactions (MCRs) are also being actively studied for the generation of artificial small-molecule libraries with high degrees of molecular diversity.[6–8] In these researches, MCRs are generally used for generation of complex molecular architectures with appendage diversity, whereas metathesis is used for skeletal diversity. A variety of biologically active compounds, useful in chemical biology studies, can be expected in such a diverse library.

In this study, we have investigated a methodology to yield skeletally different compounds from 7-oxanorbornene analogues readily available by tandem Ugi/Diels–Alder reactions,[9] through the use of a common synthetic pathway including domino metathesis as a key reaction.

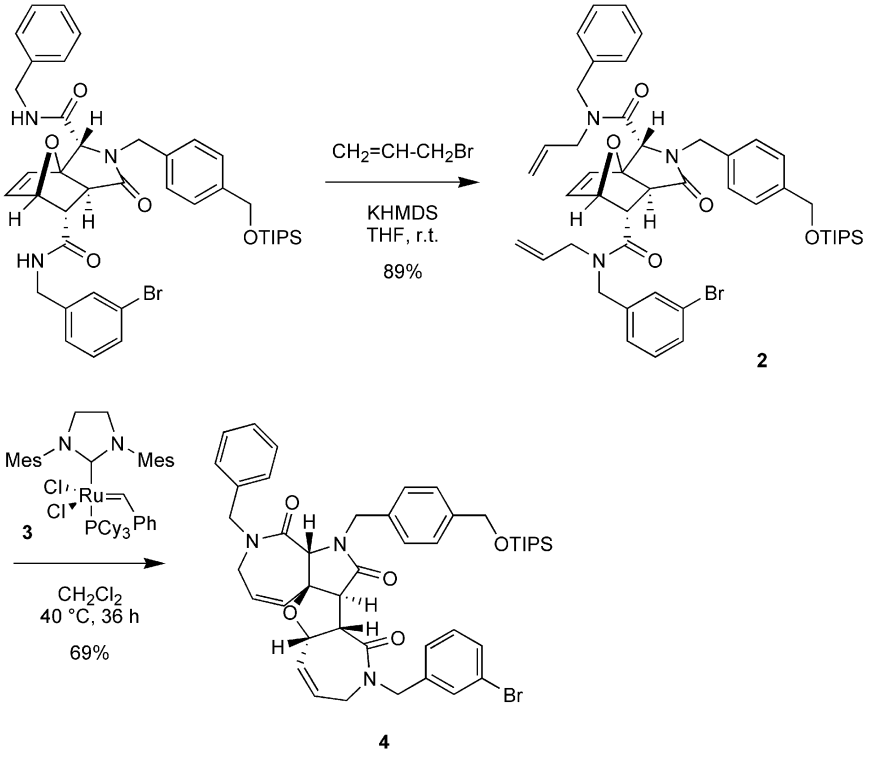
In 1999, Paulvannan reported the complexity-generating, tandem reaction between 2-furfural, benzylamine, benzyl isocyanide, and monoethyl fumarate (Scheme 1).[10,11] In this sequential transformation, an Ugi four-component coupling reaction[12] and a subsequent intramolecular Diels–Alder reaction take place quite smoothly in MeOH at room temp. to give the complex heterotricycle **1** in 89% yield. In 2000, the tandem Ugi/Diels–Alder (UDA) reaction product was transformed into the heterotetracycle **2** by Schreiber et al., who used a two-step transformation involving *N*,*N*′-bisallylation followed by ROM and RCM reactions as a complexity-enhancing sequence (Scheme 2).[6,7]



Scheme 1. Tandem Ugi/Diels–Alder reaction originally reported by Paulvannan.[10]

Our aim in this research is to control skeletal and appendage diversities generated in these processes by using "σ-elements", different appendages that pre-encode skeletal information.[7,13,14] Our ideas on these diversity-oriented synthesis (DOS) processes[14,15] are shown in Scheme 3: if the *N*-allylation of the tandem UDA reaction product **A** can be controlled in a regioselective manner by some σ-elements, then different types of heterobicycles **D** and/or heterotricycles **E** and **F** should be readily accessible by a common series of reactions. In addition, because this class of domino metathesis reaction includes CM reactions with various olefin compounds, appendage diversity should be

[a] Graduate School of Life Sciences, Tohoku University, Aoba-ku, Sendai 981-8555, Japan
Fax: +81-22-717-8827
E-mail: mao@bios.tohoku.ac.jp
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.



Scheme 2. A precedent for diversity-oriented synthesis leading to complex skeleton **4**.[6]

also introducible into the substituents **X** in **D**, **E**, and **F** by this process. Here we report our efforts directed toward the syntheses of the heterotricycles **E** and **F** by a common pathway;[9] synthetic study of the heterobicycle **D** will be published elsewhere.[16] Evaluation of the chemical space of the products expected by these DOS processes is also included in the Supporting Information.

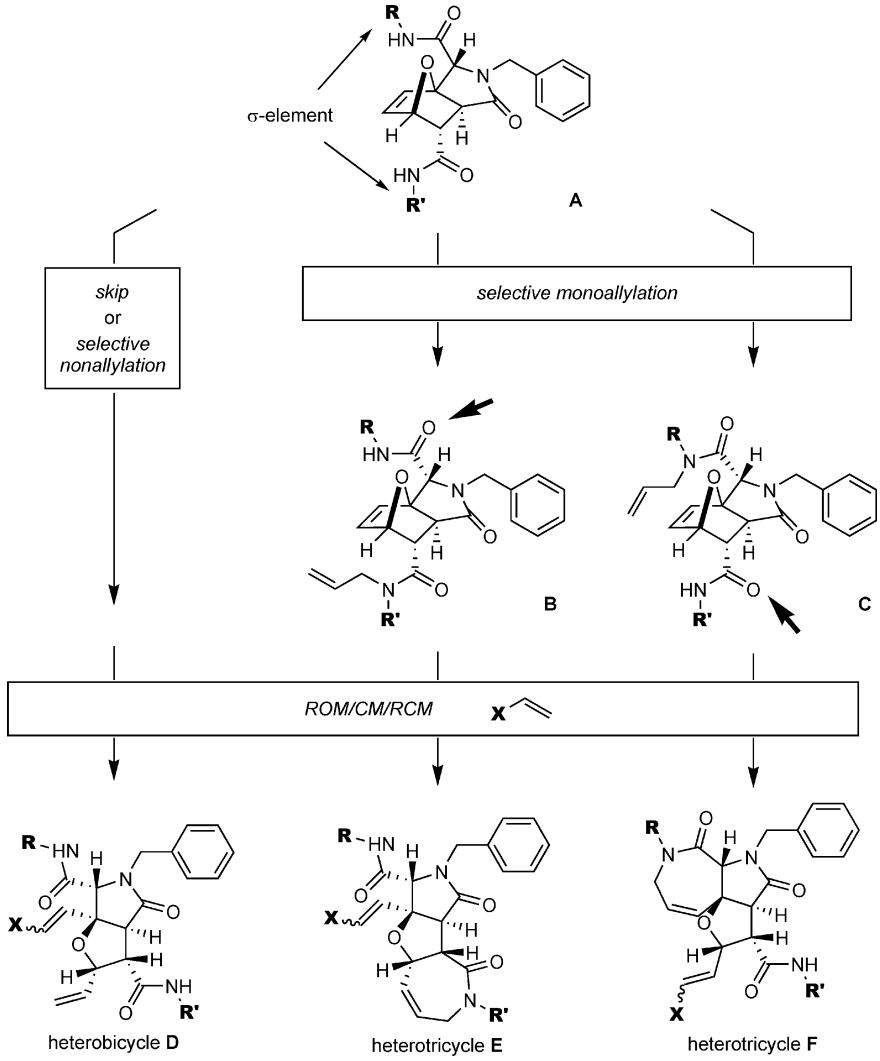
This study has also provided a possible key for understanding reactivity difference in the domino metathesis reactions of 7-oxanorbornenes. We observed that reaction yields were apparently different between two types of 7-oxanorbornenes: the **B**-type compounds are excellent substrates but the **C**-type compounds are poor, whereas the regioselectivities in the ROM reactions are excellent for both substrates. It was speculated from this that exocyclic amide carbonyl groups associate with the ruthenium metal center of the metathesis catalyst, and that the lower "*N*-monoalkyl (or -aryl)" amide carbonyl group in **C** (indicated by an arrow in Scheme 3) deactivates the catalyst activity through the association, while this is not the case for the upper "*N*-monoalkyl (or -aryl)" amide carbonyl group in **B** (indicated by an arrow). It is proposed here that the associations in intermediates derived from **B**-type and **C**-type compounds are loose and rather tight, respectively, as discussed in the final section.

Results and Discussion

At first we explored possible reaction conditions for the synthesis of the **F**-type heterotricycle **6** from the known starting tandem UDA reaction product **1** (Scheme 4).[10] Allylation of the amide functionality by the reported procedure (allyl bromide, KDMDS, THF, room temp.)[6] was found to cause decomposition of **1**. Other *N*-allylation conditions were therefore extensively examined, and we finally found that the combination of allyl bromide and CsOH (THF, room temp., 14 h)[7] gave the desired *N*-allylamide **5** in 78% yield without significant decomposition.

ROM of **5** followed by RCM in the presence of the second-generation Grubbs catalyst (**3**) was next investigated.[17] A group led by Blechert has actively studied the metathesis transformation of the 7-oxanorbornene scaffold.[2,18] Metathesis of **5** was at first attempted under less dilute conditions in CH_2Cl_2 at room temp. When the catalyst **3** (10 mol-%) was applied to **5** at a concentration of 0.03 M, the desired **F**-type heterotricycle **6** was obtained in only 20% yield. Because undesirable ring-opening metathesis polymerization (ROMP) was suspected (from thin-layer chromatography monitoring of the reaction), the reaction was next carried out under higher-dilution conditions (0.46 mM). In this case, catalyst **3** (30 mol-%) was used, and the yield of **6** was found to be improved to 54%, although the polar ROMP product was still detectable by TLC. ROMP can be generally suppressed by the addition of olefin (e.g., ethylene) to the reaction mixture so that the metathesis sequence can be terminated before the polymerization takes place.[4] We decided to optimize the reaction conditions later to improve the yield with more complex substrate **24** (see below).

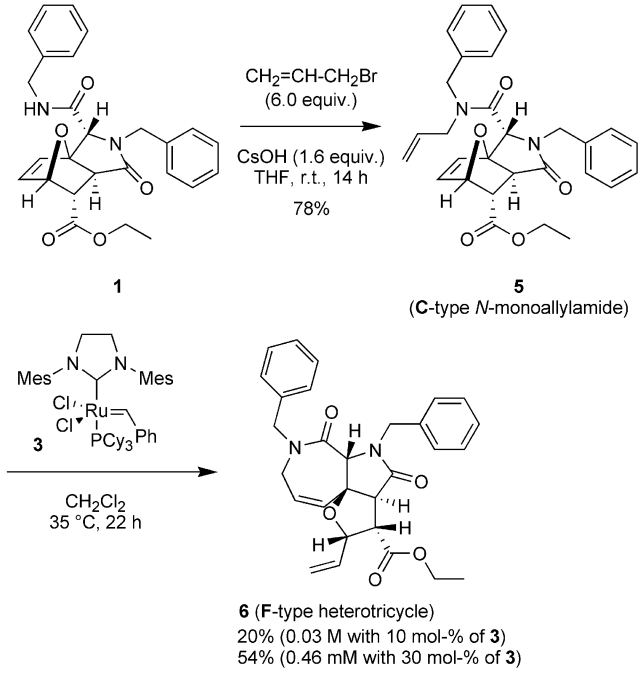
The *N*-alkyl (or -aryl) group is the σ-element[7,13,14] for the regiospecific *N*-allylation of the tandem UDA reaction product **A** shown in Scheme 3. Generally, *N*-phenylamide



Scheme 3. Our approach to various skeletons **D**–**F** from tandem UDA reaction product **A**. Arrows in **B** and **C** indicate the possible interacting group with a ruthenium metal center in the metathesis reactions.

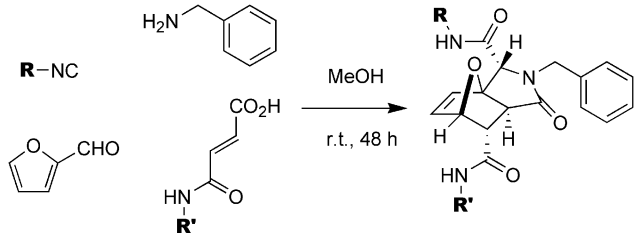
(anilide) exhibits stronger acidity than *N*-alkylamide; the pK_a values for protons of *N*-phenyl acetamide and *N*-methyl acetamide, for example, are reported to be 15.1 and 16.6, respectively.[19] We anticipated that the two amide groups indicated by arrows in the UDA product **A** (Scheme 3), derived from isocyanide and fumarate components, would be essentially differentiated if an appropriate combination of alkyl and aryl groups were used for the R and R′ groups, since the more acidic *N*-phenylamide group should be rather reactive in the *N*-allylation. On the basis of this hypothesis, we prepared eight UDA products **16**–**23**, in which anilide groups were systematically introduced (Table 1). 2-Furfural and benzylamine were used for aldehyde and amine components, respectively. Of the four isocyanides **7**–**10** used, benzyl isocyanide (**8**) and 4-methoxyphenyl isocyanide (**10**) were purchased, whereas the other two isocyanides **7** and **9** were prepared from the corresponding anilines by two-step reactions involving formylation (HCOOH, Ac_2O, pyridine, THF, 0 °C→ room temp.) and dehydration ($POCl_3$, Et_3N, CH_2Cl_2, 0 °C).[20] As carboxylic acid components, five fumaric acid monoamides **11**–**15** were prepared from commercially available monoethyl fumarate in one-pot operations involving acid chloride formation [$(COCl)_2$, DMF, benzene, 0 °C, 2 h, then concentration] followed by amidation and hydrolysis (RNH_2, Cs_2CO_3, THF, room temp., 12 h, then KOH, H_2O, room temp., 12 h).[21]

All tandem UDA reactions were carried out by mixing equimolar amounts of the four components in MeOH and stirring at room temp. for 48 h. The reaction mixtures were then concentrated and purified to give the products **16**–**23** in 32–93% yields. Since the yields of the UDA reactions generally depend on the formation of the imine intermediates (the first step in the Ugi MCR),[21] the low yields observed especially in runs 1, 3, 5, and 6 should be improved by the use of large excesses (20 equiv.)[21,22] of amine, isocyanide, and carboxylic acid components relative to 2-furfural. The structure of all products were spectroscopically determined by analogy with the authentic compounds reported previously by us.[21]



Scheme 4. A preliminary study for the synthesis of the **F**-type heterotricycle **6** from **1**.

Table 1. Preparation of the tandem UDA reaction products **16**–**23**.[a]



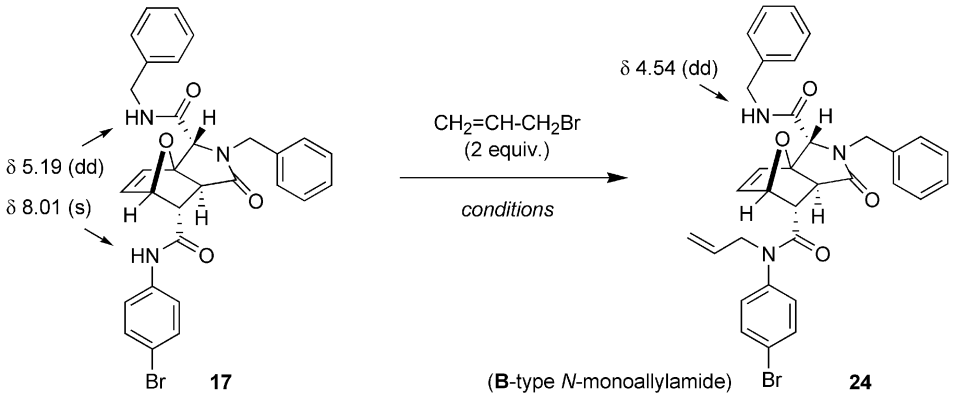
Run	R (isocyanide)	R′ (fumaric acid)	Product	Yield (%)
1	4-bromophenyl (**7**)	benzyl (**11**)	**16**	45
2	benzyl (**8**)	4-bromophenyl (**12**)	**17**	88
3	4-chlorophenyl (**9**)	benzyl (**11**)	**18**	32
4	benzyl (**8**)	4-chlorophenyl (**13**)	**19**	63
5	4-methoxyphenyl (**10**)	benzyl (**11**)	**20**	40
6	benzyl (**8**)	4-methoxyphenyl (**14**)	**21**	35
7	benzyl (**8**)	4-nitrophenyl (**15**)	**22**	93
8	benzyl (**8**)	benzyl (**11**)	**23**	87

[a] The four components were used in equimolar amounts for the reaction.

Selective procedures for mono-*N*-allylation of the tandem UDA reaction products were carefully investigated, since the method shown in Scheme 4 generally induces allylation of *N*-alkylamide, and hence was not expected to be applicable to the chemoselective allylation of *N*-arylamide over *N*-alkylamide. The substrate used for this experimentation was **17**, bearing both *N*-monoalkyl and *N*-monoarylamides, from which the **B**-type product **24** was expected on selective *N*-allylation. The results are summarized in Table 2. In these experiments, allyl bromide (2 equiv.) was ?used in various solvents (THF, Et_2O, CH_3CN, H_2O). Most of these, other than H_2O, are less polar than DMF, which is frequently used for global *N*-alkylation, so that selective reactions might take place. At first, LiOH (8 equiv.) was employed as a base. Although in THF at 0 °C (run 1) no reaction took place, the desired monoallylated product **24** was obtained after 72 h under improved conditions (Et_2O/H_2O 1:2 as a solvent at room temp.; run 2). The structure of **24** was determined from its ^{1}H NMR spectrum: most importantly a singlet anilide proton of **17** (δ = 8.01 ppm) disappeared, whereas a double doublet *N*-benzylamide proton was preserved (at δ = 4.54 ppm) in **24**. Neither K_2CO_3 nor Cs_2CO_3 was effective at all in THF/CH_3CN (1:1), with only **17** being recovered (runs 3 and 4). When CsOH (2 equiv.) was employed in THF at 0 °C, the chemospecific mono-*N*-allylation proceeded smoothly in the highest yield (79%, run 5). The reaction was clean, and the undesired *N*,*N*′-diallylamide was obtained only in a trace amount (<5% yield). Under aprotic conditions with $KN(TMS)_2$, only significant decomposition was observed (run 6).

With this optimized procedure for the chemospecific *N*-monoallylation to hand, we then carried out allylations of other tandem UDA reaction products **16** and **18**–**23** (Table 3). All reactions were performed under the conditions shown in run 5 in Table 2. The allylation of **16**, in which the anilide group is located at a different position relative to that in **17**, gave the **C**-type *N*-monoallylamide **25** in 86% yield (run 1, Table 3). In this reaction, neither the **B**-type regioisomer nor the diallylated product **G** was obtained at all. Thus, just like that of **17**, the reaction of **16** is highly chemospecific, indicating unambiguously that in the reactants **16** and **17** the regiochemistry is controlled by the anilide functionality and not by the 7-oxanorbornene skeleton. The structure of **25** was determined by ^{1}H NMR analysis as discussed above for **24**. The selectivity switching was also observed in two *N*-(4-chlorophenyl) amides **18** and **19**. Thus, the anilide **18** gave the **C**-type *N*-monoallylamide **26** in 51% yield (run 2), whereas the anilide **19** gave the **B**-type *N*-monoallylamide **27** in 50% yield (run 3), with high chemospecificity in both runs. Because of the lower acidity with respect to the 4-bromophenyl group, the allylations of *N*-(4-chlorophenyl) amide did not go to completion in these runs, and unreacted **18** and **19** were recovered in 11% and 26% yields, respectively. The *N*-(4-methoxyphenyl) amide **20** was allylated to give the expected **C**-type monoallylamide **28** in 45% yield (run 4), while the isomeric amide **21** was unexpectedly overalkylated to give rise to the **G**-type *N*,*N*′-diallylamide **29**, but not the expected **B**-type product, in fairly good yield (82%, run 5). Intermediary **B**-type *N*-monoallylamide was not detected in run 5 even by TLC during the reaction, indicating that the second allylation proceeds quite rapidly and is hardly suppressed under these reaction conditions. The *N*-(4-nitrophenyl) amide **22** did not undergo allylation and was recovered intact under these conditions, presumably because of the low reactivity of the generated anion, which should be deactivated by its tautomeric delocalization (run 6). The allylation of the *N*,*N*′-dibenzylamide **23** was a surprise to us; the unexpected *N*-

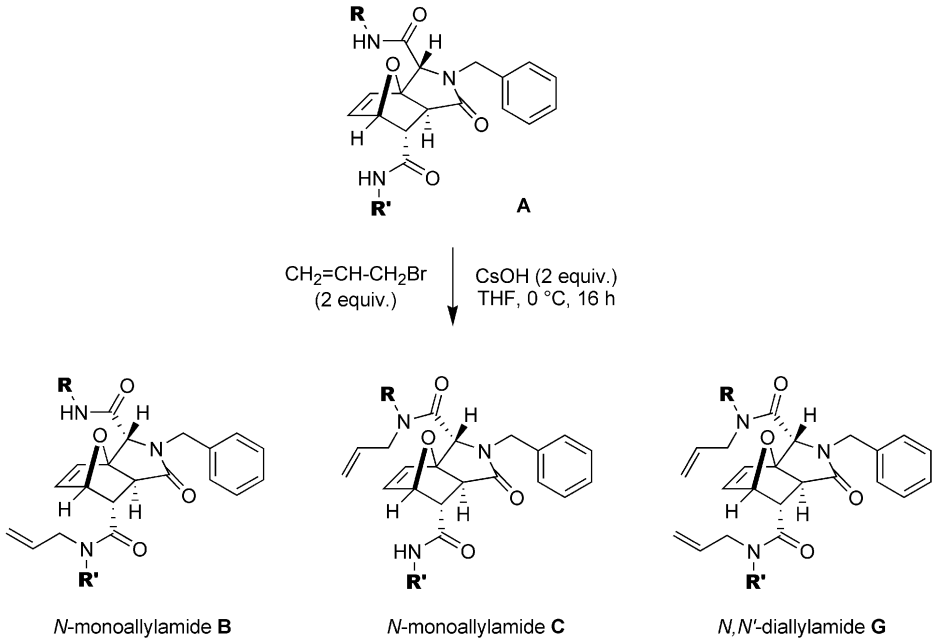
Table 2. Investigation of reaction conditions for the chemoselective *N*-monoallylation of **17** leading to the **B**-type product **24**.[a]



Run	Base (equiv.)	Solvent	Temperature	Time [h]	% Isolated yield
1	$LiOH·H_2O$ (8)	THF	0 °C	72	0
2	$LiOH·H_2O$ (8)	Et_2O/H_2O (1:2)	room temp.	72	66
3	K_2CO_3 (8)	THF/CH_3CN (1:1)	room temp.	72	0
4	Cs_2CO_3 (8)	THF/CH_3CN (1:1)	room temp.	72	0
5	CsOH (2)	THF	0 °C	16	79
6	$KN(TMS)_2$ (2)	THF	–10 °C → room temp.	16	0

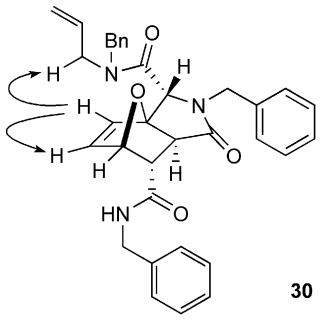
[a] δ_H values indicated in the Figure are the data collected at 300 MHz ($CDCl_3$).

Table 3. Chemospecific *N*-allylation of tandem UDA reaction products.



Run	Reactant **A**			Product distribution (% Yield)			
		R	R′	**B**	**C**	**G**	Recovered **A**
1	**16**	4-bromophenyl	benzyl	<5	86 (**25**)	<5	<5
2	**18**	4-chlorophenyl	benzyl	<5	51 (**26**)	<5	11
3	**19**	benzyl	4-chlorophenyl	50 (**27**)	<5	<5	26
4	**20**	4-methoxyphenyl	benzyl	<5	45 (**28**)	<5	25
5	**21**	benzyl	4-methoxyphenyl	<5	<5	82 (**29**)	<5
6	**22**	benzyl	4-nitrophenyl	<5	<5	<5	81
7	**23**	benzyl	benzyl	<5	34 (**30**)	<5	57

monoallylamide **30** was obtained in 34% yield with the unreacted substrate **23** recovered in 57% yield (run 7). The structure of **30** was determined by NOESY analysis (Figure 1). Though the origin for this reactivity in run 7 is not quite clear at present, it is at least obvious from this reaction that the lower exocyclic amide is essentially less reactive than the upper one, probably because of steric crowding. Optimization of the reaction conditions for a high level of chemospecificity might be further needed before the achievement of a skeletally diverse small molecule library. Nevertheless, we have thus successfully demonstrated that *N*-alkyl or *N*-arylamide components function as σ-elements in DOS on 7-oxanorbornenes.



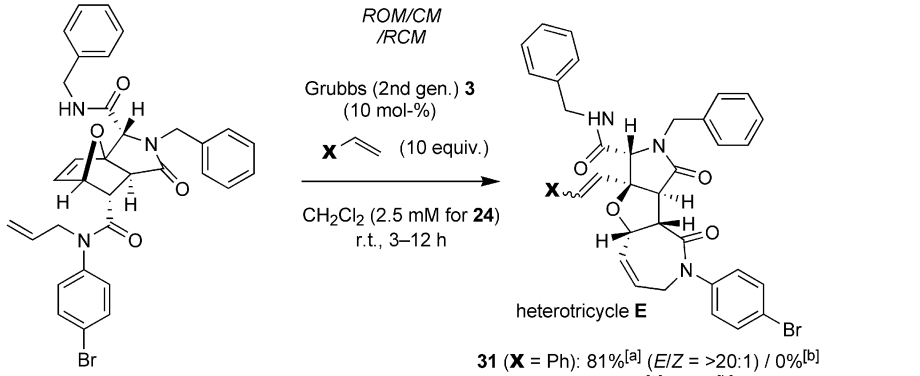
30

Figure 1. NOESY correlations observed in the *N*-monoallylamide **30**.

Metathesis reactions leading to two distinct heterotricycles **E** and **F** were next explored. Our preliminary study with the 7-oxanorbornene derivative **5** (Scheme 4) had shown that the metathesis reaction should be performed with the second-generation Grubbs catalyst **3**[17] (30 mol-%) at a concentration of 0.46 mM for **5**, preferably in the presence of the cross-metathesis reactant. On the basis of these findings, we examined several sets of reaction conditions for the ROM/CM/RCM reaction of the **B**-type *N*-monoallylamide **24**, and finally found that the use of catalyst **3** (10 mol-%) and styrene (10 equiv.) in CH_2Cl_2 (2.5 mM for **24**) at room temp. smoothly converted **24** into the **E**-type heterotricycle **31** in 81% yield (Scheme 5). As expected, the addition of styrene greatly suppressed the undesirable formation of ROMP product. It should be noted that the reaction did not take place if the concentration of **24** was lower (0.3 mM). The structure of **31** was determined by extensive NMR measurements and LC-MS analyses; most importantly, COSY and TOCSY spectra were used to determine the ^1H–^1H connectivity. The *E*/*Z* ratio was >20:1 for **31** as judged from ^1H NMR spectra. While allyl bromide is not effective as a CM reactant and no reaction was observed for **32**, the use of but-3-enyl bromide and pent-4-enyl bromide afforded the corresponding heterotricycles **33** and **34** in 81% and 82% yields, respectively. The low reactivity of allyl bromide is assumed to be attributable to steric repulsion.

The isomeric **C**-type 7-oxanorbornene **25** was next subjected to the ROM/CM/RCM reaction in the presence of three CM reactants (Scheme 6). Though these reactions with **25** were found to be sluggish and large amounts of **25** was recovered, especially for the syntheses of **36** (69%) and **37** (55%), the desired tricyclic compounds **F** (**35**–**37**) were selectively obtained in all cases. It should be noted that use of prolonged reaction times did not improve the yields, and the recovered **25** indicates that the catalyst **3** was deactivated during the reaction; the yield may therefore be improvable by use of a more sustainable metathesis catalyst such as Hoveyda–Grubbs catalyst.[23] The **F**-type heterotricycles **35**–**37** were characterized by extensive NMR and LC-MS analyses. Here, COSY and TOCSY spectra again played an important role in determination of the molecular skeletons.

We have thus developed a common pathway for the conversion of 7-oxanorbornenes (**24**, **25**) into the two skeletally distinct heterotricyclic systems **E** (**31**, **33**, **34**) and **F** (**35**–**37**) with different appendages. As stated above, this strategy should also provide the heterobicycles **D** and heterotetracycles (such as **4**) by the same series of reactions. It is noteworthy that a collection of compounds prepared by this method is reasonably diverse as judged from principal com-

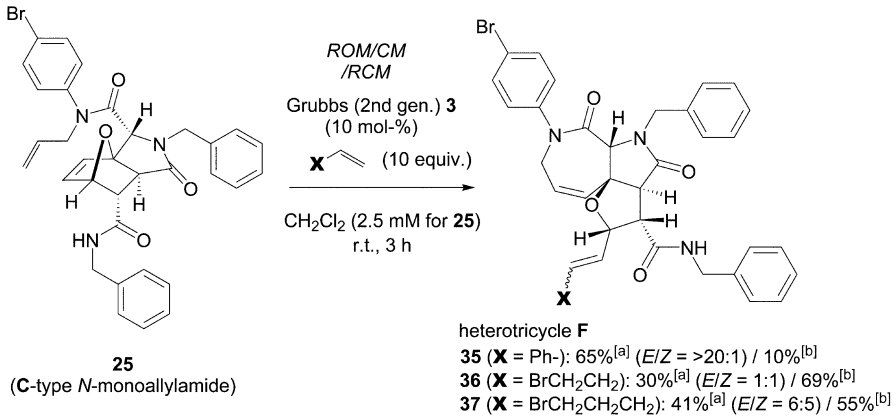


24
(**B**-type *N*-monoallylamide)

heterotricycle **E**

31 (**X** = Ph): 81%[a] (*E*/*Z* = >20:1) / 0%[b]
32 (**X** = $BrCH_2$): 0%[a] / 67%[b]
33 (**X** = $BrCH_2CH_2$): 81%[a] (*E*/*Z* = 3:2) / 15%[b]
34 (**X** = $BrCH_2CH_2CH_2$): 82%[a] (*E*/*Z* = 2:1) / 10%[b]

Scheme 5. Metathesis on **24** (**B**-type reactant) in the presence of four CM reactants leading to the **E**-type heterotricycles. [a] Isolated yield. [b] Yield for recovered **24**.



Scheme 6. Metathesis on **25** (**C**-type reactant) in the presence of three CM reactants leading to the **F**-type heterotricycles. [a] Isolated yield. [b] Yield for recovered **25**.

ponent analysis (see the Supporting Information). This is particularly advantageous in terms of chemical biology, since molecular diversity is one of the key elements for a discovery of new useful compounds from *small-molecule libraries of limited size* through biological assays.[14,24]

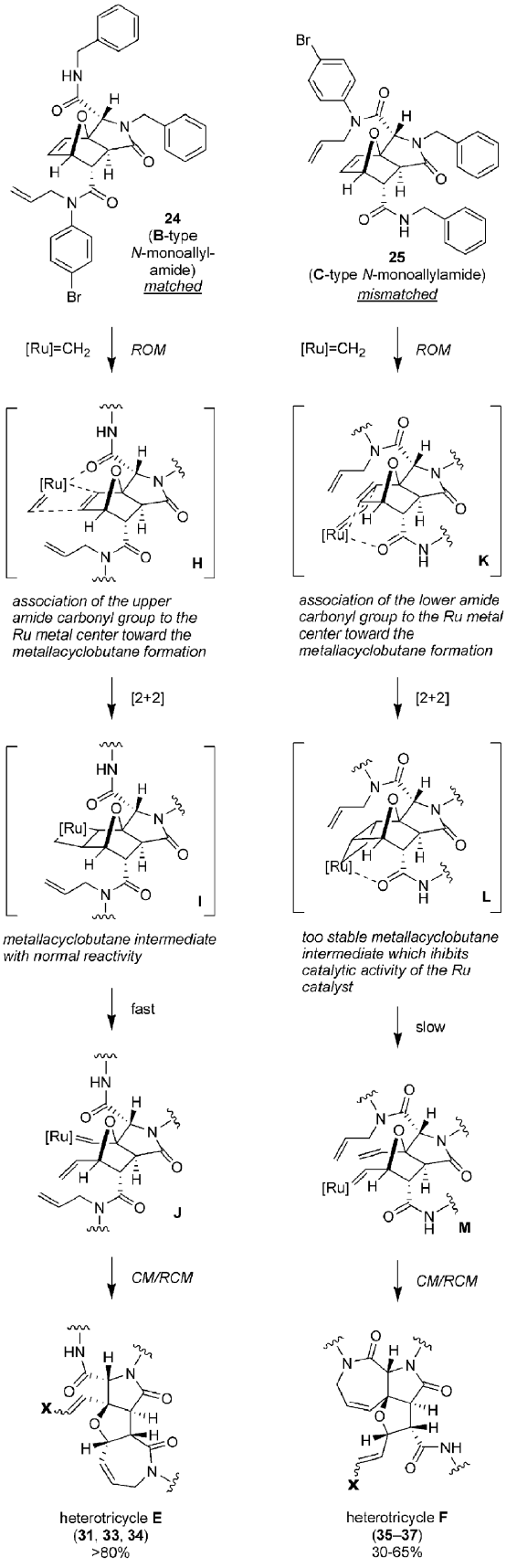
The yields for these domino metathesis reactions leading to two distinct skeletons **E** and **F** might suggest the reaction mechanism (Scheme 7). The yields for the **E**-type heterotricycles **31**, **33**, and **34** are more than 80%, whereas those for the **F**-type heterotricycles **35**–**37** are apparently lower (30–65%). Importantly, the unreacted substrates were recovered intact after the reactions in reasonable yields in most cases, showing that the first metathesis reaction determines the overall domino transformation. Since we have recently found that the domino metathesis of the **B**-type *N*-monoallylamide (such as **24**) proceeds in the order ROM/CM/RCM,[16] the difference in yields must indicate that "the first ROM reaction" takes place more rapidly in the 7-oxanorbornene skeleton of **24** than in that of **25**: the **B**-type norbornene **24** would be a *matched* substrate and the **C**-type norbornene **25** would be a *mismatched* substrate.

Fürstner et al. have reported a regiospecific RCM reaction controlled by a directing effect of an internal carbonyl group.[25] Similar types of interactions have also been reported by Cossy (ester carbonyl group),[26] Grubbs (amide carbonyl group),[27] and Tayler (hydroxy group)[28] in CM reactions.[29] Our domino metathesis sequence would also be such a case, and at present we speculate that an *N*-monoalkylamide, rather than a sterically crowding *N*-allyl-*N*-arylamide, associates with the ruthenium metal center to guide the reaction course. The proposed mechanism is shown in Scheme 7. For the mechanism of the reaction of **B**-type norbornene **24** it is speculated that the [Ru]=CH_2 approaches from the less hindered upper side of the norbornene skeleton with the guidance of the exocyclic amide carbonyl group (intermediate **H**). The effect of the association becomes weak as the metallacyclobutane intermediate **I** forms because of the geometrical strain caused by a fused tetracyclic system.[30] ROM thus takes place smoothly to generate the Ru-alkylidene species **J**, which in turn undergoes CM and RCM, giving rise to the **E**-type heterotricycles **31**, **33**, and **34**.

On the other hand, the mechanism for the domino metathesis reaction of the **C**-type norbornene **25** is speculated to be as follows. The [Ru]=CH_2 presumably approaches from the lower side of the norbornene skeleton, since the upper side is shielded by the *N*-allyl-*N*-arylamide group. The metallacyclobutane formation is guided by the association of the lower exocyclic amide carbonyl group as shown by **K**, giving rise to the intermediate **L**. In **L**, the association between the amide carbonyl functionality and the ruthenium metal center would be rather stable relative to that in **I**, and so the subsequent metathesis reactions including CM and RCM should be inhibited.[26–30] In summary, two obstacles should reduce the reaction rate and the overall conversion yield of **25** into the **F**-type heterotricycles **35**–**37**: 1) the rather crowding reaction site at the lower side of the norbornene skeleton (the intermediate **K**), and 2) inhibition of the activity of the ruthenium metal catalyst **3** by the formation of too stable metallacyclobutane intermediate **L**. The structures for metallacyclobutanes **I** and **L**, optimized at the PM3 level of theory, also support these speculations.[30]

These mechanistic considerations are also in good agreement with the predominant formation of heterotricycles **E** and **F** without isomers such as **E′** and **F′** (Figure 2), which indicates that the first ROM reaction takes place regioselectively. This is particularly noteworthy, since ROM of norbornenes is, in general, poorly regioselective.[5,29,31] In this context, we have further studied the associating effects of neighboring carbonyl functional groups in the domino metathesis of 7-oxanorbornenes, and have found that the effect essentially provides high level of regioselectivity in this reaction.[16]

However, it should be noted here that a mechanism based on [2+2] cycloaddition/cycloreversion[5] can be also operative in the reaction of **C**-type 7-oxanorbornene **25**. In this mechanism, the first ROM reaction by [Ru]=CH_2 takes place in an unselective manner, and all reaction intermediates finally lead to thermodynamically stable **F**-type prod-



Scheme 7. Proposed association mechanisms of the exocyclic amide carbonyl group with the ruthenium metal center during the first ROM reactions to account for the difference in yields.

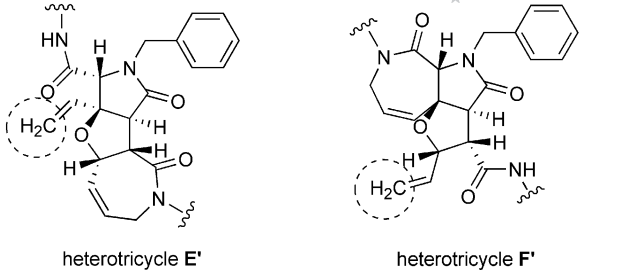


Figure 2. Heterotricycles **E**′ and **F**′ potentially generated by unselective ROM process.

ucts **35**–**37** by the well-known Chauvin mechanism.[32] Studies to elucidate the mechanisms of the domino metathesis reactions of functionalized 7-oxanorbornenes are in progress.

Conclusions

In conclusion, we have shown the potential for the associating effect between the amide carbonyl group and the ruthenium metal center to affect the reaction rate and the yield in the ROM of 7-oxanorbornenes. Here, the lower exocyclic carbonyl group in the **C**-type 7-oxanorbornene (such as in **25**) may inhibit the reaction by forming a stable chelate with a ruthenium metal center, whereas this is not the case for the upper exocyclic carbonyl group in the **B**-type 7-oxanorbornene (such as in **24**). This type of association would also be expected with use of a "regioselective" ROM reaction. Indeed, we have recently successfully demonstrated the usefulness of this effect in the development of biologically active glutamate analogues.[16] Regiocontrol is one of the major concerns in metathesis reactions.[5,25–28] Works directed towards the use of the associating effect in other types of metathesis reactions are in progress.

Through the use of the domino metathesis reaction, this study has also developed a common pathway for the synthesis of skeletally distinct heterotricycles **E** and **F** from the structurally complex starting tandem Ugi/Diels–Alder reaction product **A** (Scheme 3). Though the selectivity-controlling factor in the *N*-allylation is not quite definitive at the moment and some reactions are not complete after 16 h, all allylation reactions were found to proceed regiospecifically under identical reaction conditions. This methodology is thus expected to be useful for the construction of skeletally diverse small-molecule libraries with a variety of appendages, used for biological assays.

Experimental Section

General: All reactions sensitive to air or moisture were carried out under argon in oven-dried glassware unless otherwise noted. Anhydrous dichloromethane (CH_2Cl_2), acetonitrile (MeCN), and tetrahydrofuran (THF) were purchased from Kanto Chemical Co., Inc., Wako Pure Chemical Industries, Ltd. or Aldrich Chemical Co., and were used without further drying. Benzyl isocyanide (**8**) and 4-methoxyphenyl isocyanide (**10**) were purchased from Tokyo Chemi-

cal Industry Co., Ltd. (TCI) and Aldrich Co., respectively. The 2nd-generation Grubbs catalyst (**3**, [246047-72-3])[17] was purchased from Aldrich Co. Instant buffer (pH 7.0, TCI) was used to quench reactions where stated. All other reagents were used as supplied unless otherwise stated. Analytical thin-layer chromatography (TLC) was performed with E. Merck silica gel 60 F_{254} pre-coated plates (0.25 mm thickness). For column chromatography, Fuji Silysia silica gel BW-300 (200–400 mesh) was used. For reversed-phase column chromatography, Wako gel 100C18 (63–212 μm) was used. IR spectra were recorded with a JASCO FT/IR-4100 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Gemini 2000 or Unity INOVA 500 or INOVA 600 spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with reference to internal residual solvent [^{1}H NMR: $CHCl_3$ (δ = 7.24 ppm), CHD_2OD (δ = 3.30 ppm), C_6HD_5 (δ = 7.15 ppm), HDO (δ = 4.70 ppm). ^{13}C NMR: $CDCl_3$ (δ = 77.0 ppm), CD_3OD (δ = 49.8 ppm), C_6D_6 (δ = 128.0 ppm)]. The following abbreviations are used to designate the multiplicities; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br. = broad. High-resolution mass spectrometry (HRMS) for ESI (electrospray ionization) was recorded on a Bruker Daltonics microTOF focus mass spectrometer fitted with an Agilent HPLC system (1100 series).

C-Type *N*-Monoallyl Amide 5: Allyl bromide (0.239 mL, 2.615 mmol) and CsOH (110.0 mg, 0.698 mmol) were added at room temp. to a stirred solution of the tandem UDA reaction product **1**[10] (194.6 mg, 0.436 mmol) in THF (1.5 mL). After stirring for 14 h, the mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL). The extract was dried with Na_2SO_4 and concentrated in vacuo to give the residue, which was purified by column chromatography on silica gel (5.0 g, benzene/Et_2O 1:1) to give the *N*-monoallylamide **5** (163.4 mg, 73%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–7.05 (m, 10 H), 6.25 (dt, J = 5.7, 1.5 Hz, 1 H), 6.15 (dd, J = 5.7, 0.9 Hz, 1 H), 5.33 (m, 1 H), 5.22 (d, J = 1.5 Hz, 1 H), 5.20 (d, J = 15.0 Hz, 1 H), 5.04 (d, J = 14.1 Hz, 1 H), 4.95 (d, J = 12.0 Hz, 1 H), 4.90 (d, J = 15.3 Hz, 1 H), 4.43 (s, 1 H), 4.17 (d, J = 12.9 Hz, 1 H), 4.11 (q, J = 7.2 Hz, 1 H), 4.09 (d, J = 12.9 Hz, 1 H), 3.85 (d, J = 15.3 Hz, 1 H), 3.68 (dd, J = 18.0, 4.8 Hz, 1 H), 3.55–3.45 (m, 2 H), 3.15 (d, J = 3.9 Hz, 1 H), 1.24 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 173.4, 170.2, 167.1, 136.8, 135.4, 133.4, 131.1, 128.9, 128.8, 128.3, 128.0, 127.8, 127.6, 126.4, 91.7, 80.2, 61.2, 59.2, 58.9, 50.6, 49.4, 46.7, 45.4, 14.2 ppm. IR (film): $\tilde{\nu}$ = 3064, 3029, 2980, 2927, 1735, 1699, 1661, 1448, 1211, 702 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{29}H_{31}N_2O_5$ $[M + H]^+$ 487.2227; found 487.2215.

F-Type Heterotricycle 6: Second-generation Grubbs catalyst (**3**,[17] 20 mg, 0.024 mmol) was added at 35 °C to a stirred solution of the *N*-monoallylamide **5** (52.4 mg, 0.11 mmol) in CH_2Cl_2 (24 mL). After stirring for 22 h, the mixture was concentrated in vacuo and purified by column chromatography on silica gel (2.6 g, benzene/Et_2O 85:15) to give the heterotricycle **6** (28.4 mg, 54%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.19 (m, 10 H), 6.39 (d, J = 10.8 Hz, 1 H), 5.90 (m, 1 H), 5.75 (ddd, J = 17.3, 10.0, 9.9 Hz, 1 H), 5.34 (d, J = 15.9 Hz, 1 H), 5.28 (d, J = 17.3 Hz, 1 H), 5.18 (d, J = 10.0 Hz, 1 H), 4.69 (d, J = 15.0 Hz, 1 H), 4.67 (s, 1 H), 4.46 (d, J = 15.0 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 1 H), 4.01 (dd, J = 14.8, 4.2 Hz, 1 H), 3.78 (d, J = 7.5 Hz, 1 H), 3.39 (s, 1 H), 3.22 (q, J = 8.4 Hz, 1 H), 1.28 (t, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2, 171.0, 168.0, 136.4, 135.7, 133.9, 133.4, 128.8, 128.7, 128.4, 127.8, 127.8, 118.3, 83.3, 82.1, 64.4, 61.2, 54.8, 54.8, 53.3, 51.1, 46.2, 41.9, 14.2 ppm. IR (film): $\tilde{\nu}$ = 2980, 2927, 1733, 1700, 1699, 1450, 1233, 1184, 1029, 736, 701 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{29}H_{31}N_2O_5$ $[M + H]^+$ 487.2227; found 487.2224.

4-Bromophenyl Isocyanide (7): A solution of formic acid (99%, 0.82 mL) in Ac_2O (2.05 mL) was added dropwise at 0 °C to a stirred solution of 4-bromoaniline (1.50 g, 8.72 mmol) in pyridine (5.0 mL) and THF (25.0 mL). DMAP (20 mg) was added to the mixture, which was then allowed to warm to room temp. After 19 h, instant buffer (pH 7.0, 30 mL) was introduced, and the mixture was extracted with EtOAc (3 × 50 mL). The combined extracts were washed successively with hydrochloric acid (2 M, 2 × 50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated in vacuo to give crude *N*-(4-bromophenyl)formamide (1.01 g) as a colorless solid.

$POCl_3$ (0.310 mL, 3.24 mmol) was added at 0 °C to a stirred solution of crude *N*-(4-bromophenyl)formamide (546.9 mg) as synthesized above and Et_3N (0.750 mL, 5.46 mmol) in CH_2Cl_2 (23.0 mL). After 90 min, aqueous Na_2CO_3 (10%, 30 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were dried with Na_2SO_4 and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (10 g, benzene) to give 4-bromophenyl isocyanide (**7**, 447.2 mg, 2.46 mmol, 52% for 2 steps) as a colorless solid. The spectroscopic data were in good agreement with those reported.[33]

4-Chlorophenyl Isocyanide (9): 4-Chloroaniline (1.24 g, 7.97 mmol) was treated to give 4-chlorophenyl isocyanide (**9**, 765 mg, 71%), as a green solid, by the same procedure as used for the synthesis of **7**. The spectroscopic data were in good agreement with those reported.[33]

Fumaric Acid Mono-*N*-benzylamide (11): $(COCl)_2$ (0.543 mL, 6.22 mmol) was added at room temp. to a stirred solution of monoethyl fumarate (500 mg, 3.47 mmol) and *N*,*N*-dimethylformamide (0.015 mL) in benzene (10 mL). After 4 h, the reaction mixture was concentrated in vacuo to give a residue, which was dissolved in THF (10 mL). Benzylamine (0.493 mL, 4.51 mmol) and Cs_2CO_3 (1.13 g, 3.47 mmol) were added successively at room temp. and with vigorous stirring to the crude acyl chloride. The reaction was slightly exothermic. After 10 h, insoluble materials were filtered off, and the filtrate was concentrated to a volume of approximately 3 mL. Aqueous KOH (1 M, 7 mL, 7 mmol) was added at room temp. to the stirred mixture. After the resultant brown mixture had been stirred for 4 h, it was washed with Et_2O (5 mL). Et_2O (3 mL) and hydrochloric acid (2 M, 7 mL, 14 mmol) were added to the aqueous layer with vigorous stirring. The immediately generated white precipitates were collected by filtration, washed with Et_2O, and dried under high vacuum to give fumaric acid mono-*N*-benzylamide (**11**, 495 mg, 70%) as a white powder: ^{1}H NMR (600 MHz, CD_3OD): δ = 8.99 (br. s, 1 H), 7.33–7.24 (m, 5 H), 7.00 (d, J = 15.5 Hz, 1 H), 6.71 (d, J = 15.5 Hz, 1 H), 4.46 (m, 2 H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 169.2, 167.0, 140.2, 138.3, 132.5, 130.5, 129.5, 129.2, 45.2 ppm. IR (KBr): $\tilde{\nu}$ = 3293, 3085, 3132, 1689, 1651, 1556, 1416, 1336, 1263, 1244, 984, 719, 695 cm^{-1}. HRMS (ESI, negative) calcd. for $C_{11}H_{10}NO_3$ $[(M - H)^-]$ 204.0666; found 204.0661.

Fumaric Acid Mono-*N*-(4-bromophenyl)amide (12): Monoethyl fumarate (480 mg, 3.33 mmol) was treated by the same procedure as used for the synthesis of **11**, to give fumaric acid mono-*N*-(4-bromophenyl) amide (**12**, 681 mg, 76%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.61 (d, J = 7.5 Hz, 2 H), 7.47 (d, J = 7.5 Hz, 2 H), 7.14 (dd, J = 10.0, 2.5 Hz, 2 H), 6.80 (d, J = 13.0 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 169.1, 165.0, 139.6, 138.6, 133.7, 133.3, 123.7, 119.0 ppm. IR (KBr): $\tilde{\nu}$ = 3303, 1693, 1665, 1594, 1530, 1489, 1397, 1334, 989, 822 cm^{-1}. HRMS (ESI, negative) calcd. for $C_{10}H_7BrNO_3$ $[(M - H)^-]$ 267.9615; found 267.9612.

Fumaric Acid Mono-*N*-(4-chlorophenyl)amide (13): Monoethyl fumarate (1.00 g, 6.94 mmol) was treated by the same procedure as used for the synthesis of **11**, to give fumaric acid mono-*N*-(4-chlorophenyl) amide (**13**, 1.37 g, 87%) as a white solid. ^{1}H NMR (300 MHz, CD_3OD): δ = 7.66 (d, J = 9.3 Hz, 2 H), 7.33 (d, J = 9.3 Hz, 2 H), 7.15 (d, J = 15.6 Hz, 1 H), 6.80 (d, J = 15.6 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 169.0, 164.9, 139.1, 138.6, 133.2, 131.4, 130.7, 123.3 ppm. IR (KBr): $\tilde{\nu}$ = 3304, 1663, 1645, 1531, 989, 824, 688 cm^{-1}. HRMS (ESI, negative) calcd. for $C_{10}H_7ClNO_3$ [(M – H)$^-$] 224.0120; found 224.0121.

Fumaric Acid Mono-*N*-(4-methoxyphenyl)amide (14): Monoethyl fumarate (480 mg, 3.33 mmol) was treated by the same procedure as used for the synthesis of **11**, to give fumaric acid mono-*N*-(4-methoxyphenyl) amide (**14**, 732 mg, 100%) as a white solid. ^{1}H NMR (500 MHz, CD_3OD): δ = 7.56 (d, J = 9.0 Hz, 1 H), 7.15 (d, J = 15.5 Hz, 1 H), 6.90 (d, J = 9.0 Hz, 1 H), 6.77 (d, J = 15.5 Hz, 1 H), 3.78 (s, 3 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 169.3, 164.6, 159.2, 139.0, 133.2, 132.6, 123.7, 115.6, 56.7 ppm. IR (KBr): $\tilde{\nu}$ = 3292, 1658, 1644, 1513, 1246, 1031, 830 cm^{-1}. HRMS (ESI, negative) calcd. for $C_{11}H_{10}NO_4$ [(M – H)$^-$] 220.0615; found 220.0614.

Fumaric Acid Mono-*N*-(4-nitrophenyl)amide (15): Monoethyl fumarate (1.00 g, 6.94 mmol) was treated by the same procedure as used for the synthesis of **11**, to give fumaric acid mono-*N*-(4-nitrophenyl) amide (**15**, 1.63 g, 100%) as a yellow solid. ^{1}H NMR (600 MHz, CD_3OD): δ = 8.24 (dd, J = 8.4 Hz, 2 H), 7.91 (dd, J = 8.4 Hz, 2 H), 7.16 (d, J = 15.6 Hz, 1 H), 6.86 (d, J = 15.6 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, CD_3OD): δ = 169.0, 165.3, 146.4, 145.8, 138.0, 134.3, 126.6, 121.5 ppm. IR (KBr): $\tilde{\nu}$ = 3368, 3334, 1691, 1613, 1557, 1496, 1329, 1254, 1161, 1113, 976, 852 cm^{-1}. HRMS (ESI, negative) calcd. for $C_{10}H_7N_2O_5$ [(M – H)$^-$] 235.0360; found 235.0360.

Tandem UDA Reaction Product 16: 2-Furfural (0.0199 mL, 0.24 mmol), benzylamine (0.026 mL, 0.24 mmol), 4-bromophenyl isocyanide (**7**, 43.7 mg, 0.24 mmol), and fumaric acid mono-*N*-benzylamide (**11**, 55.9 mg, 0.24 mmol) were mixed and stirred in MeOH (1.5 mL) at room temp. for 48 h. After concentration in vacuo, the mixture was purified by column chromatography on silica gel (2.5 g, hexane/EtOAc 1:2) to give the tandem UDA reaction product **16** (51.5 mg, 45%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, J = 8.7 Hz, 2 H), 7.34–7.17 (m, 12 H), 6.51 (dd, J = 5.9, 1.5 Hz, 1 H), 6.39 (d, J = 6.0 Hz, 1 H), 6.14 (br. t, 1 H), 5.20 (d, J = 4.8 Hz, 1 H), 4.85 (d, J = 15.3 Hz, 1 H), 4.42 (dd, J = 15.0, 5.4 Hz, 1 H), 4.30 (dd, J = 15.0, 5.4 Hz, 1 H), 4.27 (d, J = 15.3 Hz, 1 H), 4.22 (s, 1 H), 3.33 (t, J = 4.5 Hz, 1 H), 2.92 (d, J = 3.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 169.9, 165.3, 137.8, 136.7, 136.3, 134.7, 131.7 (2 C), 128.6, 128.4, 128.1, 127.8, 127.7, 127.5, 127.2, 121.4, 91.8, 80.6, 63.1, 52.2, 48.0, 45.7, 43.5 ppm. IR (film): $\tilde{\nu}$ = 3254, 1695, 1662, 1490, 1276, 702 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{30}H_{27}BrN_3O_4$ [M + H]$^+$ 572.1185; found 572.1179.

Tandem UDA Reaction Product 17: 2-Furfural (0.0167 mL, 0.20 mmol) was treated by the same procedure as used for the synthesis of **16**, to give the tandem UDA reaction product **17** (101 mg, 88%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (br. s, 1 H), 7.40–7.13, (m, 14 H), 6.51 (dd, J = 5.7, 1.8 Hz, 1 H), 6.30 (d, J = 5.7 Hz, 1 H), 6.09 (br. t, J = 6.0 Hz, 1 H), 5.19 (dd, J = 4.4, 1.5 Hz, 1 H), 4.97 (d, J = 15.0 Hz, 1 H), 4.43 (dd, J = 9.3, 5.7 Hz, 1 H), 4.33 (dd, J = 9.3, 5.7 Hz, 1 H), 4.09 (s, 1 H), 4.04 (d, J = 15.0 Hz, 1 H), 3.43 (t, J = 4.5 Hz, 1 H), 2.97 (d, J = 4.5 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7, 167.9, 166.6, 137.1, 136.8, 135.6, 134.7, 132.8, 131.7, 128.9, 128.8, 128.0, 127.9, 127.8, 127.7, 121.4, 116.8, 91.9, 80.7, 63.3, 52.2, 49.0, 45.9, 43.8 ppm. IR (film): $\tilde{\nu}$ = 3258, 3114, 2871, 1669, 1587, 1486, 1395, 821 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{30}H_{27}BrN_3O_4$ [M + H]$^+$ 572.1185; found 572.1179.

Tandem UDA Reaction Product 18: 2-Furfural (0.0199 mL, 0.24 mmol) was treated by the same procedure as used for the synthesis of **16**, to give the tandem UDA reaction product **18** (40.6 mg, 32%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45 (br. s, 1 H), 7.36–7.19 (m, 14 H), 6.53 (dd, J = 11.4, 1.5 Hz, 1 H), 6.41 (d, J = 6.0 Hz, 1 H), 6.15 (br. t, 1 H), 5.22 (dd, J = 4.8, 1.8 Hz, 1 H), 4.87 (d, J = 15.0 Hz, 1 H), 4.44 (dd, J = 14.7, 5.7 Hz, 1 H), 4.32 (dd, J = 14.7, 5.7 Hz, 1 H), 4.29 (d, J = 15.0 Hz, 1 H), 4.24 (s, 1 H), 3.34 (t, J = 3.0 Hz, 1 H), 2.94 (d, J = 3.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 169.9, 165.4, 137.8, 131.7, 129.8, 129.6, 128.4, 127.6, 127.4, 127.1, 125.8, 121.0, 91.8, 80.6, 63.0, 52.1, 47.9, 45.7, 43.5 ppm. IR (film): $\tilde{\nu}$ = 3064, 3030, 2924, 1684, 1494, 700 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{30}H_{27}ClN_3O_4$ [M + H]$^+$ 528.1690; found 528.1696.

Tandem UDA Reaction Product 19: 2-Furfural (0.0199 mL, 0.24 mmol) was treated by the same procedure as used for the synthesis of **16**, to give the tandem UDA reaction product **19** (79.5 mg, 63%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.28 (br. s, 1 H), 7.40–7.11 (m, 14 H), 6.43 (d, J = 5.7 Hz, 1 H), 6.30 (d, J = 5.7 Hz, 1 H), 6.28 (br. t, J = 6.0 Hz, 1 H), 5.14 (dd, J = 4.0, 1.8 Hz, 1 H), 4.95 (d, J = 15.6 Hz, 1 H), 4.42 (dd, J = 14.6, 5.7 Hz, 1 H), 4.35 (dd, J = 14.6, 5.7 Hz, 1 H), 4.12 (s, 1 H), 4.01 (d, J = 15.6 Hz, 1 H), 3.42 (t, J = 4.5 Hz, 1 H), 3.02 (d, J = 4.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7, 168.1, 166.5, 137.1 136.4, 134.7, 132.4, 129.2, 128.9 (2 C), 128.8, 128.0, 127.8, 121.1, 111.9, 91.8, 80.7, 63.3, 52.6, 49.2, 46.0, 43.9 ppm. IR (film): $\tilde{\nu}$ = 3088, 3063, 3031, 2924, 1669, 1418, 1399, 1241, 699 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{30}H_{26}ClN_3O_4$ [M + H]$^+$ 528.1685; found 528.1699.

Tandem UDA Reaction Product 20: 2-Furfural (0.0167 mL, 0.20 mmol) was treated by the same procedure as used for the synthesis of **16**, to give the tandem UDA reaction product **20** (43.0 mg, 40%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (br. s, 1 H), 7.34–7.16 (m, 12 H), 6.81 (d, J = 5.4 Hz, 2 H), 6.39 (t, J = 4.0 Hz, 1 H), 6.37 (br. t, 1 H), 6.34 (d, J = 3.6 Hz, 1 H), 5.13 (d, J = 2.1 Hz, 1 H), 4.93 (d, J = 9.6 Hz, 1 H), 4.36 (dd, J = 9.0, 3.6 Hz, 1 H), 4.24 (s, 1 H), 4.22 (dd, J = 9.0, 3.9 Hz, 1 H), 4.10 (d, J = 9.6 Hz, 1 H), 3.77 (s, 3 H), 3.27 (t, J = 2.7 Hz, 1 H), 2.95 (d, J = 2.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 169.6, 164.7, 157.1, 137.8, 136.4, 135.0, 132.7, 129.6, 129.0, 128.7, 128.1 (2×), 127.7, 127.6, 121.9, 114.2, 91.7, 80.6, 64.1, 55.5, 52.4, 48.5, 46.3, 43.7 ppm. IR (film): $\tilde{\nu}$ = 3083, 3030, 2931, 1653, 1511, 1243, 700 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{31}H_{30}N_3O_5$ [M + H]$^+$ 524.2180; found 524.2190.

Tandem UDA Reaction Product 21: 2-Furfural (0.0199 mL, 0.24 mmol) was treated by the same procedure as used for the synthesis of **16**, to give the tandem UDA reaction product **21** (44.1 mg, 35%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.08 (br. s, 1 H), 7.33–7.10 (m, 12 H), 6.77 (d, J = 9.0 Hz, 2 H), 6.60 (br. s, 1 H), 6.42 (dd, J = 3.2, 1.5 Hz, 1 H), 6.27 (d, J = 6.0 Hz, 1 H), 5.12 (dd, J = 2.7, 1.5 Hz, 1 H), 4.90 (d, J = 15.9 Hz, 1 H), 4.39 (dd, J = 15.0, 6.3 Hz, 1 H), 4.32 (dd, J = 15.0, 6.3 Hz, 1 H), 4.13 (s, 1 H), 3.98 (d, J = 15.9 Hz, 1 H), 3.74 (s, 3 H), 3.38 (t, J = 4.2 Hz, 1 H), 3.01 (d, J = 4.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.7, 168.0, 166.6, 156.4, 137.2, 136.6, 134.8, 132.3, 130.8, 128.9 (2 C), 128.0 (3 C), 127.9, 121.8, 114.0, 91.7, 80.7, 63.3, 55.4, 52.8, 49.2, 46.0, 43.9 ppm. IR (film): $\tilde{\nu}$ = 3063, 3031, 2928,

1684, 1511, 1243, 749, 699 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{31}H_{30}N_3O_5$ [M + H]$^+$ 524.2180; found 524.2199.

Tandem UDA Reaction Product 22: 2-Furfural (0.0199 mL, 0.24 mmol) was treated by the same procedure as used for the synthesis of **16**, to give the tandem UDA reaction product **22** (127 mg, 93%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.29 (br. s, 1 H), 8.12 (d, J = 8.1 Hz, 2 H), 7.64 (d, J = 8.1 Hz, 2 H), 7.37–7.12 (m, 10 H), 6.45 (dd, J = 6.0, 1.5 Hz, 1 H), 6.30 (d, J = 6.0 Hz, 1 H), 6.29 (br. t, 1 H), 5.18 (dd, J = 4.4, 1.2 Hz, 1 H), 5.00 (d, J = 15.3 Hz, 1 H), 4.44 (dd, J = 14.4, 5.7 Hz, 1 H), 4.37 (dd, J = 14.4, 5.7 Hz, 1 H), 4.13 (s, 1 H), 4.04 (d, J = 15.3 Hz, 1 H), 3.50 (t, J = 4.2 Hz, 1 H), 3.08 (d, J = 4.2 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.8, 166.7, 166.6, 144.2, 143.0, 137.4, 135.7, 134.5, 132.5, 132.2, 128.5, 127.7, 127.6, 127.4, 124.6, 119.0, 92.1, 80.6, 62.6, 52.0, 52.0, 45.7, 43.5 ppm. IR (film): $\tilde{\nu}$ = 3088, 3064, 2927, 1684, 1506, 1335, 1172, 699 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{30}H_{27}N_4O_6$ [M + H]$^+$ 539.1925; found 539.1941.

Tandem UDA Reaction Product 23: 2-Furfural (0.0199 mL, 0.24 mmol) was treated by the same procedure as used for the synthesis of **16**, to give the tandem UDA reaction product **23** (105 mg, 87%) as a yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.13 (m, 15 H), 6.50 (d, J = 5.7 Hz, 1 H), 6.30 (d, J = 6.3 Hz, 1 H), 6.11 (br. t, 1 H), 5.95 (br. t, 1 H), 5.17 (dd, J = 8.4, 1.8 Hz, 1 H), 4.93 (d, J = 15.3 Hz, 1 H), 4.64–4.28 (m, 4 H), 4.05 (d, J = 15.3 Hz, 1 H), 3.31 (t, J = 4.2 Hz, 1 H), 2.86 (d, J = 4.8 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.9, 169.8, 166.8, 137.8, 137.4, 136.1, 134.6, 131.9, 128.5, 128.5, 128.3, 127.7, 127.6, 127.6, 127.4 (2 C), 127.1, 91.7, 80.5, 62.6, 51.9, 47.8, 45.6, 43.4, 43.3 ppm. IR (film): $\tilde{\nu}$ = 3088, 3064, 2925, 1653, 1243, 943, 699 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{31}H_{30}N_3O_4$ [M + H]$^+$ 508.2231; found 508.2238.

B-Type *N*-Monoallylamide 24: CsOH (5.9 mg, 0.078 mmol) was added at 0 °C to a stirred solution of the tandem UDA reaction product **17** (22.5 mg, 0.039 mmol) and allyl bromide (3.5 μL, 0.078 mmol) in THF (1.0 mL). After the mixture had been stirred for 16 h, saturated aqueous NH_4Cl (5 mL) was added, and the mixture was extracted with EtOAc (10 mL). The extract was dried with Na_2SO_4 and concentrated in vacuo, and the residue was purified by column chromatography on silica gel (1.0 g, hexane/EtOAc 2:1) to give the *N*-monoallylamide **24** (19.3 mg, 79%) as a colorless solid. The structure of **24** was determined by ^{1}H NMR analysis (see text). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (d, J = 7.6 Hz, 2 H), 7.34–7.08 (m, 12 H), 6.41 (d, J = 5.7 Hz, 1 H), 6.20 (dd, J = 5.7, 1.5 Hz, 1 H), 6.04 (br. t, J = 5.7 Hz, 1 H), 5.77 (ddd, J = 17.4, 10.2, 7.2 Hz, 1 H), 5.12 (d, J = 10.2 Hz, 1 H), 5.03 (d, J = 17.1 Hz, 1 H), 4.80 (d, J = 14.7 Hz, 1 H), 4.54 (dd, J = 4.4, 1.2 Hz, 1 H), 4.35 (t, J = 4.5 Hz, 2 H), 4.19 (t, J = 6.6 Hz, 2 H), 4.05 (d, J = 14.7 Hz, 1 H), 4.03 (s, 1 H), 3.30 (t, J = 3.6 Hz, 1 H), 3.25 (d, J = 3.3 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.2, 168.0, 166.5, 140.4, 137.1, 135.0, 134.3, 133.5, 133.2, 132.2, 128.9 (2 C), 128.1, 127.9, 127.8, 122.5, 118.8, 92.2, 80.5, 63.3, 53.0, 51.5, 46.2, 45.8, 43.8 ppm. IR (film): $\tilde{\nu}$ = 3064, 3030, 2925, 1694, 1661, 1407, 1220, 729 cm^{-1}. HRMS (ESI) calcd. for $C_{33}H_{31}BrN_3O_4$ [M + H]$^+$ 612.1498; found 612.1492.

C-Type *N*-Monoallylamide 25: Compound **16** (15.6 mg, 0.027 mmol) was treated by the same procedure as used for the synthesis of **24**, to give the *N*-monoallylamide **25** (14.5 mg, 86%) as a colorless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.22 (m, 10 H), 7.07 (m, 2 H), 6.59 (m, 2 H), 6.59 (dd, J = 4.2, 1.5 Hz, 1 H), 6.40 (d, J = 6.0 Hz, 1 H), 6.23 (br. t, 1 H), 5.7 (ddd, J = 16.8, 9.9, 6.6 Hz, 1 H), 5.14 (dd, J = 3.6, 1.8 Hz, 1 H), 5.14 (d, J = 9.6 Hz, 1 H), 5.05 (d, J = 17.1 Hz, 1 H), 4.77 (d, J = 15.3 Hz, 1 H), 4.42 (dd, J = 14.6, 5.7 Hz, 1 H), 4.30 (dd, J = 14.6, 5.7 Hz, 1 H), 4.29 (d, J = 15.3 Hz, 1 H), 4.15 (s, 1 H), 4.01 (ddd, J = 17.4, 10.8, 6.9 Hz, 1 H), 3.26 (t, J = 4.8 Hz, 1 H), 2.91 (d, J = 5.1 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.5, 170.1, 166.5, 139.0, 137.8, 136.9, 134.9, 132.9, 132.0, 131.5, 129.4, 91.2, 80.5, 59.6, 53.3, 52.7, 48.5, 45.9, 43.6 ppm. IR (film): $\tilde{\nu}$ = 3088, 3064, 3031, 2926, 1669, 1418, 1222, 701 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{33}H_{31}BrN_3O_4$ [M + H]$^+$ 612.1498; found 612.1492.

C-Type *N*-Monoallylamide 26: Compound **18** (12.7 mg, 0.024 mmol) was treated by the same procedure as used for the synthesis of **24**, to give the *N*-monoallylamide **26** (6.9 mg, 51%) as a colorless solid. Unreacted **18** (1.4 mg, 11%) was also recovered. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.07 (m, 14 H), 6.58 (d, J = 5.4 Hz, 1 H), 6.40 (d, J = 6.0 Hz, 1 H), 6.27 (m, 1 H), 5.72 (m, 1 H), 5.15 (d, J = 10.5 Hz, 1 H), 5.05 (d, J = 17.1 Hz, 1 H), 4.78 (d, J = 15.3 Hz, 1 H), 4.42 (dd, J = 15.2, 6.0 Hz, 1 H), 4.29 (dd, J = 15.2, 6.0 Hz, 1 H), 4.26 (t, J = 4.2 Hz, 1 H), 4.14 (s, 1 H), 4.09 (d, J = 15.3 Hz, 1 H), 3.26 (t, J = 4.8 Hz, 1 H), 2.91 (d, J = 4.8 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 3086, 3064, 2921, 1671, 1491, 1424, 1247, 701 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{33}H_{31}ClN_3O_4$ [M + H]$^+$ 568.1998; found 568.2003.

B-Type *N*-Monoallylamide 27: Compound **19** (24.0 mg, 0.045 mmol) was treated by the same procedure as used for the synthesis of **24**, to give the *N*-monoallylamide **27** (12.9 mg, 50%) as a colorless solid. Unreacted **19** (6.2 mg, 26%) was also recovered. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.07 (m, 14 H), 6.40 (d, J = 6.0 Hz, 1 H), 6.19 (d, J = 6.0 Hz, 1 H), 6.12 (br. t, J = 5.4 Hz, 1 H), 5.77 (m, 1 H), 5.11 (d, J = 10.2 Hz, 1 H), 5.03 (d, J = 17.1 Hz, 1 H), 4.80 (d, J = 15.3 Hz, 1 H), 4.53 (d, J = 4.2 Hz, 1 H), 4.38 (dd, J = 14.6, 6.0 Hz, 1 H), 4.31 (dd, J = 14.6, 6.0 Hz, 1 H), 4.18 (t, J = 5.4 Hz, 2 H), 4.03 (s, 1 H), 4.02 (d, J = 15.3 Hz, 1 H), 3.30 (t, J = 3.6 Hz, 1 H), 3.26 (d, J = 3.6 Hz, 1 H) ppm. IR (film): $\tilde{\nu}$ = 3031, 2926, 1671, 1413, 1220, 713 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{33}H_{31}ClN_3O_4$ [M + H]$^+$ 568.1998; found 568.2016.

C-Type *N*-Monoallylamide 28: Compound **20** (15.2 mg, 0.030 mmol) was treated by the same procedure as used for the synthesis of **24**, to give the *N*-monoallylamide **28** (7.6 mg, 45%) as a colorless solid. Its ^{1}H NMR spectrum indicated that **28** was obtained as a mixture of two diastereomeric isomers (3:1) at the *N*-allyl-*N*-arylamide moiety. Unreacted **20** (4.2 mg, 25%) was also recovered. ^{1}H NMR (600 MHz, $CDCl_3$, for the major isomer): δ = 7.34–6.81 (m, 14 H), 6.57 (dd, J = 5.7, 1.6 Hz, 1 H), 6.43 (d, J = 5.7 Hz, 1 H), 6.39 (dd, J = 5.9, 5.9 Hz, 1 H), 5.74 (m, 1 H), 5.16–5.12 (m, 2 H), 5.05 (dd, J = 17.2, 1.2 Hz, 1 H), 4.77 (d, J = 15.4 Hz, 1 H), 4.41 (dd, J = 14.5, 5.9 Hz, 1 H), 4.31–4.25 (m, 2 H), 4.20 (s, 1 H), 4.10–4.06 (m, 2 H), 3.71 (s, 3 H), 3.26 (dd, J = 4.6, 4.6 Hz, 1 H), 2.93 (d, J = 4.6 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, for the major isomer): δ = 174.5, 170.2, 166.9, 159.2, 137.8, 136.7, 135.1, 132.6, 132.5, 131.9, 128.9, 128.6, 128.6, 128.1, 127.9, 127.6, 127.4, 119.3, 114.1, 91.3, 80.3, 59.6, 55.3, 53.3, 52.9, 48.6, 45.9, 43.5 ppm. IR (KBr): $\tilde{\nu}$ = 3309, 1689, 1606, 1511, 1441, 1332, 1298, 1247, 1172, 1031, 731, 702 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{34}H_{34}N_7O$ [M + H]$^+$ 564.2493; found 564.2489.

G-Type *N*,*N*′-Diallylamide 29: Compound **21** (14.2 mg, 0.027 mmol) was treated by the same procedure as used for the synthesis of **24**, to give the *N*,*N*′-diallylamide **29** (13.1 mg, 82%) as a yellow amorphous solid. Its ^{1}H NMR spectrum indicated that **29** was obtained as a mixture of two diastereomeric isomers (1:1) at the *N*-allyl-*N*-benzylamide moiety: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–6.79 (m, 14 H), 6.54–6.08 (m, 3 H), 5.83–5.74 (m, 2 H), 5.24–4.77 (m, 4 H), 4.50–4.02 (m, 8 H), 4.83 and 4.76 (s, 3 H total),

3.90–2.93 (m, 3 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, for both isomers): δ = 174.6, 174.2, 168.3, 167.5, 167.0, 166.7, 159.1, 155.4, 138.0, 137.6, 135.4, 135.2, 134.8, 134.1, 133.7, 133.7, 133.3, 133.1, 132.5, 132.2, 132.0, 130.7, 128.7, 128.4, 128.4, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 127.3, 127.2, 127.1, 121.3, 121.2, 118.1, 114.8, 113.4, 113.4, 92.0, 91.8, 81.0, 80.2, 63.3, 63.0, 55.3, 55.2, 53.0, 52.9, 51.2, 50.7, 48.4, 48.0, 45.9, 45.9, 45.8, 45.2, 43.3, 43.2 ppm. IR (film): $\tilde{\nu}$ = 2960, 1684, 1511, 1244, 1029, 701 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{37}H_{38}N_3O_5$ [M + H]$^+$ 604.2806; found 604.2803.

C-Type *N*-Monoallylamide 30: Compound **23** (15.6 mg, 0.031 mmol) was treated by the same procedure as used for the synthesis of **24**, to give the *N*-monoallylamide **30** (5.4 mg, 34%) as a colorless amorphous solid. ^{1}H NMR spectrum indicated that **30** was obtained as a mixture of two diastereomeric isomers (2:1) at the *N*-allyl-*N*-benzylamide moiety. The structure was determined by NOESY analysis (see text). Unreacted **23** (8.9 mg, 57%) was also recovered. ^{1}H NMR (600 MHz, $CDCl_3$, for the major isomer): δ = 7.36–6.85 (m, 15 H), 6.54–6.51 (m, 2 H), 6.09 (d, *J* = 5.9 Hz, 1 H), 5.36 (m, 1 H), 5.19–5.13 (m, 1 H), 5.09 (d, *J* = 14.4 Hz, 1 H), 4.97 (d, *J* = 10.4 Hz, 1 H), 4.91 (d, *J* = 17.0 Hz, 1 H), 4.45 (s, 1 H), 4.41 (m, 1 H), 4.30 (dd, *J* = 14.7, 5.4 Hz, 1 H), 4.06 (d, *J* = 14.4 Hz, 1 H), 3.85 (d, *J* = 15.4 Hz, 1 H), 3.70 (br. d, *J* = 17.7 Hz, 1 H), 3.51 (dd, *J* = 17.7, 5.0 Hz, 1 H), 3.33 (dd, *J* = 8.4, 4.3 Hz, 1 H), 2.85 (d, *J* = 4.3 Hz, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$, for the major isomer): δ = 174.1, 170.1, 166.9, 137.8, 137.2, 136.6, 135.0, 131.8, 130.9, 128.9, 128.8, 128.7, 128.6, 128.0, 127.9, 127.7, 127.6, 127.4, 117.6, 91.1, 80.3, 59.5, 53.2, 49.2, 48.4, 48.3, 45.5, 43.5 ppm. IR (film): $\tilde{\nu}$ = 3064, 3030, 2921, 1662, 1452, 1220, 701 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{34}H_{34}N_3O_4$ [M + H]$^+$ 548.2544; found 548.2568.

E-Type Heterotricycle 31: Styrene (43 μL, 0.38 mmol) and the second-generation Grubbs catalyst (**3**, 3.4 mg, 3.8 μmol) were added at room temp. to a stirred solution of the *N*-monoallylamide **24** (23.2 mg, 37.8 μmol) in CH_2Cl_2 (15 mL). After stirring for 12 h, the mixture was concentrated in vacuo and purified by column chromatography on silica gel (1.0 g, hexane/EtOAc 65:35) to give the heterotricycle **31** (*E* isomer only, 22.0 mg, 81%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–6.97 (m, 12 H), 6.91 (d, *J* = 14.5 Hz, 2 H), 6.60 (d, *J* = 15.6 Hz, 1 H), 6.22 (d, *J* = 15.6 Hz, 1 H), 6.18 (m, 1 H), 6.08 (d, *J* = 11.1 Hz, 1 H), 5.67 (br. t, *J* = 5.4 Hz, 1 H), 5.25 (d, *J* = 15.0 Hz, 1 H), 5.25 (d, *J* = 15.0 Hz, 1 H), 4.76 (dd, *J* = 4.5, 2.4 Hz, 1 H), 4.46 (dd, *J* = 10.5, 5.4 Hz, 1 H), 4.36 (dd, *J* = 8.4, 6.0 Hz, 1 H), 4.26 (dd, *J* = 8.4, 6.0 Hz, 1 H), 4.02 (d, *J* = 6.6 Hz, 1 H), 3.75 (s, 1 H), 3.63 (q, *J* = 8.4 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.3, 167.6, 167.3, 142.1, 136.8, 136.4, 135.3, 132.3, 132.0, 130.8, 128.9, 128.7, 128.5, 128.4, 128.0, 127.9, 127.7 (2 C), 127.6, 127.4 (2 C), 126.8, 119.9, 85.1, 77.1, 71.8, 54.9, 50.5, 46.4, 45.8, 44.0 ppm. IR (film): $\tilde{\nu}$ = 3080, 3053, 3029, 1669, 1419, 1239, 1010, 746, 699 cm^{-1}. HRMS (FAB) calcd. for $C_{39}H_{35}O_4N_3Br$ [M + H]$^+$ 688.1811; found 688.1818.

E-Type Heterotricycle 33: The *N*-monoallylamide **24** (8.4 mg, 0.015 mmol) was treated by the same procedure as used for the synthesis of **31**, except for the reaction time (3 h), to give the heterotricycle **33** (*E*/*Z* 3:2, 8.0 mg, 81%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 8.7 Hz, 5 H), 7.32–7.11 (m, 15 H), 6.99 (d, *J* = 8.7 Hz, 5 H), 6.20 (m, 2.5 H), 6.02 (br. s, 1.5 H), 5.98 (br. s, 1 H), 5.81 (br. t, *J* = 5.7 Hz, 1.5 H), 5.71 (br. t, *J* = 5.7 Hz, 1 H), 5.66–5.43 (m, 4 H), 5.19 (m, 4 H), 4.66 (dd, *J* = 6.8, 2.4 Hz, 1.5 H), 4.59 (dd, *J* = 6.8, 2.4 Hz, 1 H), 4.50–4.26 (m, 4.5 H), 4.10 (d, *J* = 5.7 Hz, 2.5 H), 3.98 (d, *J* = 6.0 Hz, 1 H), 3.85 (s, 1 H), 3.77 (d, *J* = 14.4 Hz, 1.5 H), 3.75 (d, *J* = 14.4 Hz, 1 H), 3.67 (s, 1.5 H), 3.62 (m, 2.5 H), 3.18 (t, *J* = 6.9 Hz, 2.5 H), 2.26 (quint, *J* = 7.2 Hz, 1 H), 2.12 (quint, *J* = 7.2 Hz, 1 H), 1.98–1.89 (m, 2.5 H), 1.72–1.64 (m, 5.5 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4, 174.3, 168.0, 167.6, 167.3, 167.2, 142.1, 142.0, 137.4, 137.3, 135.4, 135.3, 132.3, 132.2, 132.1 (2 C), 131.9, 130.3, 129.1, 128.9 (2 C), 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3, 120.9, 120.0, 85.3, 84.7, 72.0, 71.7, 56.3, 54.5, 50.6 (2 C), 46.4 (2 C), 45.9, 45.8, 43.9 (2 C), 34.1, 33.1 (2 C), 32.2, 31.9 (2 C), 30.2, 27.3 ppm. IR (film): $\tilde{\nu}$ = 3305, 3009, 2925, 1694, 1682, 1489, 1424, 1240, 1010, 754 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{35}H_{34}Br_2N_3O_4$ [M + H]$^+$ 718.0911; found 718.0901.

E-Type Heterotricycle 34: The *N*-monoallylamide **24** (13.7 mg, 0.0225 mmol) was treated by the same procedure as used for the synthesis of **31**, except for the reaction time (3 h), to give the heterotricycle **34** (*E*/*Z* 2:1, 13.9 mg, 82%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (d, *J* = 9.0 Hz, 6 H), 7.34–7.11 (m, 30 H), 7.00 (d, *J* = 9.0 Hz, 6 H), 6.20 (m, 3 H), 6.04 (br. s, 2 H), 6.01 (br. s, 1 H), 5.82–5.62 (m, 3 H), 5.49 (d, *J* = 15.6 Hz, 3 H), 5.62–5.29 (m, 3 H), 4.71 (dd, *J* = 6.8, 2.4 Hz, 2 H), 4.59 (dd, *J* = 6.8, 2.4 Hz, 1 H), 4.47 (m, 3 H), 4.38 (t, *J* = 6.3 Hz, 3 H), 4.08 (br. s, 2 H), 3.98 (d, *J* = 6.3 Hz, 3 H), 3.77 (d, *J* = 14.7 Hz, 3 H), 3.76 (d, *J* = 14.7 Hz, 1 H), 3.68 (s, 1 H), 3.65 (quint, *J* = 8.1 Hz, 3 H), 3.12 (m, 2 H), 2.73 (quint, *J* = 7.2 Hz, 1 H), 2.58 (quint, *J* = 7.2 Hz, 1 H), 2.42–2.19 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.4 (2 C), 168.0, 167.6, 167.3, 167.2, 142.1, 142.0, 137.3, 135.3, 132.1 (2 C), 131.9, 131.8, 129.1, 129.0, 128.9 (2 C), 128.7, 128.6, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.6, 127.5, 127.4, 127.3 (2 C), 127.1, 120.1 (2 C), 85.3, 84.7, 72.0, 71.7, 56.3, 54.5, 53.4, 50.2, 46.4, 45.8, 43.9, 34.1, 33.1, 32.8, 32.5, 32.2, 31.9, 31.6, 31.3, 30.3, 30.2, 27.3 ppm. IR (film): $\tilde{\nu}$ = 3069, 3036, 2927, 1683, 1423, 1233, 1010, 730, 700 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{36}H_{36}Br_2N_3O_4$ [M + H]$^+$ 732.1067; found 732.1063.

F-Type Heterotricycle 35: The *N*-monoallylamide **25** (7.8 mg, 0.013 mmol) was treated by the same procedure as used for the synthesis of **31**, except for the reaction time (3 h), to give the heterotricycle **35** (*E*/*Z* >20:1, 5.0 mg, 65%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–6.98 (m, 19 H), 6.11 (m, 1 H), 5.82 (br. t, *J* = 5.8 Hz, 1 H), 5.79 (m, 1 H), 5.46 (d, *J* = 15.0 Hz, 1 H), 5.27 (d, *J* = 14.1 Hz, 1 H), 5.17 (d, *J* = 10.5 Hz, 2 H), 4.47 (t, *J* = 7.5 Hz, 1 H), 4.34 (d, *J* = 5.1 Hz, 2 H), 4.10 (s, 1 H), 3.89 (d, *J* = 14.1 Hz, 1 H), 3.60 (s, 1 H), 3.32 (d, *J* = 6.9 Hz, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 174.6, 171.1, 167.0, 139.8, 137.7, 136.8, 135.3, 134.2, 132.9, 132.4, 131.7, 128.9, 128.7, 128.6, 128.5, 128.0, 66.9, 55.9, 53.6, 52.9, 45.6, 43.7 ppm. IR (film): $\tilde{\nu}$ = 3029, 2925, 1669, 1488, 1248, 1011, 700 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{39}H_{35}BrN_3O_4$ [M + H]$^+$ 688.1811; found 688.1805.

F-Type Heterotricycle 36: The *N*-monoallylamide **25** (16.6 mg, 0.0272 mmol) was treated by the same procedure as used for the synthesis of **31**, except for the reaction time (3 h), to give the heterotricycle **36** (*E*/*Z* 1:1, 5.9 mg, 30%) as a brown solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 9.0 Hz, 2 H), 7.32–7.15 (m, 12 H), 6.02–5.85 (m, 2 H), 5.69 (d, *J* = 9.6 Hz, 0.5 H), 5.68 (d, *J* = 17.1 Hz, 0.5 H), 5.23 (d, *J* = 9.6 Hz, 0.5 H), 5.19 (d, *J* = 17.1 Hz, 0.5 H), 4.52 (t, *J* = 6.9 Hz, 1 H), 4.44–4.29 (m, 2 H), 3.85 (d, *J* = 15.0 Hz, 1 H), 3.80 (s, 1 H), 3.48 (d, *J* = 10.5 Hz, 1 H), 3.36 (t, *J* = 6.3 Hz, 1 H), 3.29 (t, *J* = 5.4 Hz, 1 H), 3.15–3.00 (m, 2 H), 2.50–2.27 (m, 3 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.5, 168.4, 167.7, 165.7 (2 C), 144.3, 143.2, 135.8, 135.1 (2 C), 133.9, 133.8, 133.7, 132.9, 132.1 (2 C), 130.6, 130.2 (2 C), 130.0 (2 C), 129.0, 128.8, 128.7, 128.6, 128.5, 128.3, 128.0 (3 C), 127.7 (2 C), 121.6,

121.3, 119.5, 117.7, 86.8 (2 C), 82.7, 82.5, 72.3 (2 C), 60.8 (2 C), 55.5, 55.4, 53.9, 53.7, 46.0 (2 C), 43.9, 43.8, 35.0, 34.8, 32.2, 31.9 ppm. IR (film): $\tilde{\nu}$ = 3063, 3031, 2960, 2925, 1699, 1684, 1539, 1489, 1009, 701 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{35}H_{34}Br_2N_3O_4$ $[M + H]^+$ 718.0911; found 718.0905.

F-Type Heterotricycle 37: The *N*-monoallylamide **25** (16.1 mg, 0.0264 mmol) was treated by the same procedure as used for the synthesis of **31**, except for the reaction time (3 h), to give the heterotricycle **37** (*E*/*Z* 6:5, 7.9 mg, 41%) as a brown solid. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 9.0 Hz, 2 H), 7.32–7.15 (m, 12 H), 5.95 (br. t, *J* = 5.7 Hz, 1 H), 5.88–5.78 (m, 2 H), 5.60 (d, *J* = 15.6 Hz, 1 H), 5.55 (d, *J* = 12.3 Hz, 1 H), 5.19 (d, *J* = 12.3 Hz, 1 H), 4.51–4.26 (m, 3 H), 3.87 (d, *J* = 17.1 Hz, 1 H), 3.78 (d, *J* = 4.8 Hz, 1 H), 3.50 (br. s, 1 H), 3.37–3.28 (m, 2 H), 3.19–3.73 (m, 2 H), 2.12 (q, *J* = 7.2 Hz, 1 H), 1.94 (quint, *J* = 6.9 Hz, 1 H), 1.82 (quint, *J* = 6.9 Hz, 1 H), 1.63 (m, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.3 (2 C), 168.6, 167.6, 167.2, 165.7, 143.3, 141.3, 139.3, 137.8, 137.5, 135.7, 135.1, 134.8, 134.6, 133.6, 132.4, 132.2 (2 C), 131.6, 129.2, 129.0 (2 C), 128.9, 128.8, 128.7 (2 C), 128.6, 128.2 (2 C), 128.0 (2 C), 127.9, 126.8, 126.6, 121.3 (2 C), 117.9, 86.9, 86.7, 83.3, 82.5, 72.5 (2 C), 68.8, 67.0, 55.4 (2 C), 54.0, 46.0, 43.8 (2 C), 32.9, 32.8, 31.7, 31.4, 30.4, 30.3 ppm. IR (film): $\tilde{\nu}$ = 2956, 2931, 1700, 1684, 1540, 1489, 1244, 1009, 700 cm^{-1}. HRMS (ESI, positive) calcd. for $C_{36}H_{36}Br_2N_3O_4$ $[M + H]^+$ 732.1067; found 734.1070.

Supporting Information (see also the footnote on the first page of this article): Structures of model compounds for metallacyclobutanes **I** and **L** optimized at the PM3 level of theory, together with principal component analysis for compounds in this paper.

Acknowledgments

A research fellowship to M. I. from the Japan Society for the Promotion of Science (JSPS) is gratefully acknowledged. We thank one of the reviewers for valuable comments for possible involvement of a [2+2] cycloreversion process in the reaction of **25**.

[1] a) A. Deiters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238; b) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527; c) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243–251; d) S. Kotha, K. Lahiri, *Synlett* **2007**, 2767–2784.
[2] N. Holub, S. Blechert, *Chem. Asian J.* **2007**, *2*, 1064–1082.
[3] a) W. J. Zuercher, M. Hashimoto, R. H. Grubbs, *J. Am. Chem. Soc.* **1996**, *118*, 6634–6640; b) D. S. La, E. S. Sattely, J. G. Ford, R. R. Schrock, A. H. Hoveyda, *J. Am. Chem. Soc.* **2001**, *123*, 7767–7778.
[4] R. Stragies, S. Blechert, *Synlett* **1998**, 169–170.
[5] O. Arjona, A. G. Csaky, J. Plumet, *Eur. J. Org. Chem.* **2003**, 611–622.
[6] D. S. Lee, J. K. Sello, S. L. Schreiber, *Org. Lett.* **2000**, *2*, 709–712.
[7] J. K. Sello, P. R. Andreana, D. S. Lee, S. L. Schreiber, *Org. Lett.* **2003**, *5*, 4125–4127.
[8] A. Basso, L. Banfi, R. Riva, G. Guanti, *Tetrahedron* **2006**, *62*, 8830–8837.
[9] For our preliminary publication on this study, see: a) M. Oikawa, M. Ikoma, M. Sasaki, *Tetrahedron Lett.* **2005**, *46*, 5863–5866; b) M. Ikoma, M. Oikawa, M. Sasaki, *Tetrahedron* **2008**, *64*, 2740–2749.
[10] K. Paulvannan, *Tetrahedron Lett.* **1999**, *40*, 1851–1854.
[11] K. Paulvannan, *J. Org. Chem.* **2004**, *69*, 1207–1214.
[12] a) I. Ugi, *Angew. Chem.* **1959**, *71*, 386–386; b) I. Ugi, C. Steinbruckner, *Angew. Chem.* **1960**, *72*, 267–268.
[13] a) M. D. Burke, E. M. Berger, S. L. Schreiber, *Science* **2003**, *302*, 613–618; b) M. D. Burke, E. M. Berger, S. L. Schreiber, *J. Am. Chem. Soc.* **2004**, *126*, 14095–14104.
[14] M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58.
[15] S. L. Schreiber, *Science* **2000**, *287*, 1964–1969.
[16] M. Ikoma, M. Oikawa, M. B. Gill, G. T. Swanson, R. Sakai, K. Shimamoto, M. Sasaki, *Eur. J. Org. Chem.* **2008**, 5215–5220.
[17] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.
[18] a) S. Maechling, S. E. Norman, J. E. McKendrick, S. Basra, K. Koppner, S. Blechert, *Tetrahedron Lett.* **2006**, *47*, 189–192; b) S. Michaelis, S. Blechert, *Chem. Eur. J.* **2007**, *13*, 2358–2368.
[19] The data were collected from SciFinder Scholar **2006**; American Chemical Society (http://www.cas.org/SCIFINDER/SCHOLAR/).
[20] R. Obrecht, R. Herrmann, I. Ugi, *Synthesis* **1985**, 400–402.
[21] M. Oikawa, M. Ikoma, M. Sasaki, *Tetrahedron Lett.* **2005**, *46*, 415–418.
[22] M. Oikawa, M. Ikoma, M. Sasaki, *Tetrahedron Lett.* **2004**, *45*, 2371–2375.
[23] S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.
[24] a) C. Lipinski, A. Hopkins, *Nature* **2004**, *432*, 855–861; b) B. R. Stockwell, *Nature* **2004**, *432*, 846–854.
[25] A. Fürstner, K. Langemann, *Synthesis* **1997**, 792–803.
[26] S. BouzBouz, J. Cossy, *Org. Lett.* **2001**, *3*, 1451–1454.
[27] T. L. Choi, A. K. Chatterjee, R. H. Grubbs, *Angew. Chem. Int. Ed.* **2001**, *40*, 1277–1279.
[28] F. C. Engelhardt, M. J. Schmitt, R. E. Taylor, *Org. Lett.* **2001**, *3*, 2209–2212.
[29] In these examples, the associating effect was used to suppress the undesirable metathesis process through the formation of stable and unreactive chelates. For a review, see: S. J. Connon, S. Blechert, *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923.
[30] See Supporting Information for optimized structures.
[31] a) O. Arjona, A. G. Csaky, M. C. Murcia, J. Plumet, *J. Org. Chem.* **1999**, *64*, 9739–9741; b) P. Mayo, W. Tam, *Tetrahedron* **2002**, *58*, 9513–9525; c) J. W. Herndon, *Coord. Chem. Rev.* **2003**, *243*, 3–81.
[32] J. L. Herisson, Y. Chauvin, *Makromol. Chem.* **1971**, *141*, 161–176.
[33] A. Guirado, A. Zapata, J. L. Gomez, L. Trabalon, J. Galvez, *Tetrahedron* **1999**, *55*, 9631–9640.

Received: August 11, 2008
Published Online: November 21, 2008

