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Ruthenium-catalyzed [2+2] cycloadditions of bicyclic alkenes and ynamides

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Abstract—Ruthenium-catalyzed [2+2] cycloadditions between bicyclic alkenes and ynamides were investigated. The ynamide moiety was found to be compatible with the ruthenium-catalyzed cycloaddition conditions giving the corresponding cyclobutene cycloadducts in moderate to good yields (up to 97%). Diastereoselective cycloaddition utilizing chiral cyclic ynamides were also examined and a low to moderate level of asymmetric induction was observed.

1. Introduction

Ynamines and ynamides (electron-deficient ynamines) have been shown to be useful building blocks in organic synthesis.[1] However, their inaccessibility had limited their synthetic usefulness until recent developments and improvements in their synthesis were published by Danheiser,[2] Hsung,[3] Cossy,[4] Sato,[5] and Witulski.[6] Ynamides have been the main focus of research in this area due to their greater stability over ynamines. Accordingly, the interest in the application of ynamides in organic synthesis has increased remarkably. Recent studies on the synthetic value of ynamides include: Pauson–Khand [2+2+1] cycloadditions,[7] thermal and transition metal-catalyzed [4+2] cycloadditions,[8] Lewis acid catalyzed [2+2] cycloadditions,[9] Rh-catalyzed [2+2+2] cycloadditions,[10] ring-closing metathesis (RCM),[11] transition metal-catalyzed coupling reactions,[12] rearrangement reactions,[13] hydrometalation and hydrohalogenation reactions,[14] and cyclization reactions.[15]

We have studied various types of cycloaddition reactions of bicyclic alkenes, and are especially interested in those catalyzed by transition metals.[16,17] Transition metal-catalyzed cycloadditions have demonstrated their utility as efficient methods in the formation of rings and complex molecules.[18] We and others have studied various aspects of transition metal-catalyzed [2+2] cycloadditions between an alkene and an alkyne for the synthesis of cyclobutene rings, including development of novel catalysts, study of the intramolecular variant of the reaction, investigation of the chemo- and regioselectivity of unsymmetrical substrates, and asymmetric induction studies using chiral auxilliary on the alkyne component.[17,19–21] The alkynes employed in transition metal-catalyzed [2+2] cycloadditions usually contain carbon substituents such as alkyl, aryl, ester, and ketone functionalities. However, we recently showed that heteroatom substituted acetylenes such as alkynyl halides[17g] and ynamides[17h] were also suitable substrates. We now report a full account on the ruthenium-catalyzed [2+2] cycloaddition reactions of bicyclic alkenes with ynamides.

2. Results and discussion

2.1. Synthesis of ynamides

To begin this study, several acyclic ynamides were prepared (Table 1). Screening of various methods for the synthesis of ynamides found the methods by Danheiser[2] and Hsung[3] to be the most reliable. However, fine-tuning of the reaction conditions was required in order to optimize yields for some of the desired ynamides. For example, using Hsung's catalytic $CuSO_4$ method[3c] did not result in the formation of ynamide **3a** (entry 1), and only homo-coupling of alkynyl bromide **1a** was observed. Similarly, Danheiser's stoichiometric CuI method[2] only produced ynamide **3a** in a low yield of 16% (entry 2). Re-examination of Buchwald's amidation of aryl bromide[22] suggested that the rate of

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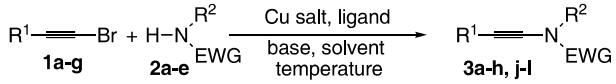
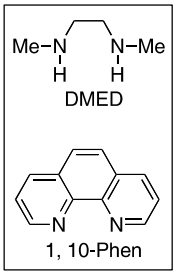
Table 1. Synthesis of acyclic ynamides **3a–h**, **3j–l**





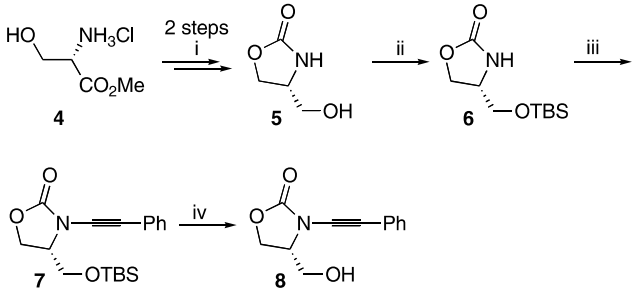
3a: R^1=Ph, EWG=COOMe, R^2=Cy
3b: R^1=Ph, EWG=COOMe, R^2=CH_2CH_2Ph
3c: R^1=Ph, EWG=COOMe, R^2=CH_2Ph
3d: R^1=Ph, EWG=COO^tBu, R^2=CH_2Ph
3e: R^1=Ph, EWG=COOMe, R^2=Ph
3f: R^1=*p*-Me-C_6H_5, EWG=COOMe, R^2=Ph
3g: R^1=*o*-Me-C_6H_5, EWG=COOMe, R^2=Ph
3h: R^1=*m*-F-C_6H_5, EWG=COOMe, R^2=Ph
3j: R^1=CH_2OTBS, EWG=COOMe, R^2=Ph
3k: R^1=CH_2CH_2OTBS, EWG=COOMe, R^2=Ph
3l: R^1=$^iPr_3Si$, EWG=COOMe, R^2=Ph

Entry	Ynamide **3**	Alkyne **1** (equiv)	Amide **2** (equiv)	Cu (equiv)	Base (equiv)	Ligand (equiv)	Solvent/ Temperature (°C)	Yield (%)[a]
1	**3a**	**1a** (2)	**2a** (1)	$CuSO_4$ (0.1)	K_2CO_3 (2.0)	Phen (0.2)	Toluene/60	0
2		**1a** (2)	**2a** (1)	CuI (1.0)	KHMDS (0.1)	—	Pyridine/25	16
3[b]		**1a** (2)	**2a** (1)	CuI (0.06)	KHMDS (1.2)	Phen (0.14)	Toluene/90	43
4[b]		**1a** (2)	**2a** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.24)	Toluene/90	65
5[b]	**3b**	**1a** (1)	**2b** (1.1)	CuI (0.06)	KHMDS (1.1)	DMED (0.1)	Toluene/90	17
6		**1a** (1)	**2b** (1.2)	CuI (0.06)	K_2CO_3 (2.0)	DMED (0.1)	Toluene/60	38
7[b]		**1a** (3)	**2b** (1)	CuI (0.08)	KHMDS (1.2)	Phen (0.12)	Toluene/90	52
8	**3c**	**1a** (2)	**2c** (1)	CuI (1.0)	KHMDS (1.0)	—	Pyridine/25	0
9		**1a** (1)	**2c** (1)	CuCN (0.06)	K_3PO_4 (2.0)	DMED (0.1)	Toluene/110	0
10[b]		**1a** (2)	**2c** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.26)	Toluene/90	61
11[b]	**3d**	**1a** (1)	**2d** (1.7)	CuI (0.2)	KHMDS (1.0)	Phen (0.22)	Toluene/90	68
12[b]	**3e**	**1a** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.24)	Toluene/90	65
13[b]	**3f**	**1b** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.27)	Toluene/90	48
14[b]	**3g**	**1c** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.2)	Phen (0.26)	Toluene/90	39
15[b]	**3h**	**1d** (2)	**2e** (1)	CuI (0.2)	KHMDS (1.1)	Phen (0.28)	Toluene/90	54
16[b]	**3j**	**1e** (1)	**2e** (1.4)	CuI (0.4)	KHMDS (1.7)	Phen (0.46)	Toluene/90	59
17[b]	**3k**	**1f** (1.4)	**2e** (1)	CuI (0.25)	KHMDS (1.0)	Phen (0.23)	Toluene/90	26
18[b]	**3l**	**1g** (1.2)	**2e** (1)	CuI (0.3)	KHMDS (1.3)	Phen (0.36)	Toluene/90	90

[a] Yield of isolated cycloadducts after column chromatography.
[b] The base was added slowly to the reaction mixture at the indicated temperature through a syringe pump over 3–4 h. See text for details.

deprotonation of the amide had to match the rate of the amidation reaction in order for the coupling reaction to be successful. Buchwald suggested that the formation of excess deprotonated amide deactivates the Cu-catalyst by forming an unreactive cuprate complex. With this insight, Hsung's catalytic CuI method[3b] was modified by adding the base (KHMDS) slowly to the reaction mixture over 3–4 h using a syringe pump. To our delight, we could improve the yield of ynamide **3a** up to 65% (entry 4). Similarly, several reaction conditions were attempted for the syntheses of ynamides **3b** and **3c** and it was found that our modified conditions gave the best results. By using the modified reaction conditions (0.2–0.3 equiv of CuI, 0.22–0.36 equiv of the 1,10-phen ligand, and adding 1.2 equiv of the base KHMDS slowly over 3–4 h in toluene at 90 °C), ynamides **3d–3l** were obtained in moderate to good yields (entries 11–18).

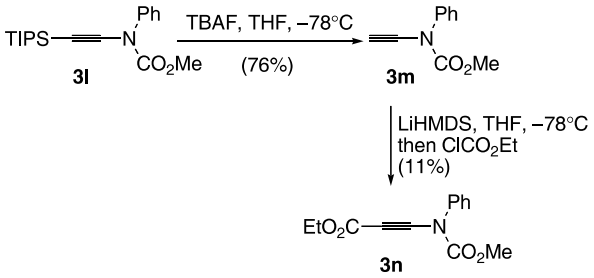
This methodology was also effective for the synthesis of the chiral ynamide **8** (Scheme 1). The synthesis first required the preparation of **5** from (*S*)-4-hydroxymethyloxazolidin-2-one **4** following a method developed by Sibi et al.[23] Direct coupling of **5** with bromophenylacetylene **1a** did not produce the desired product. However, when the alcohol group was protected using TBSCl, the coupled product **7** was obtained in 46% yield. Deprotection of **7** afforded **8** in a yield of 40%.



Scheme 1. Synthesis of (*S*)-4-hydroxymethyl-3-phenylethynyl-oxazolidin-2-one (**8**). Reagents and conditions: (i) see Ref. 34; (ii) TBSCl, DMAP, Et_3N, CH_2Cl_2, 25 °C (80%); (iii) **1a**, CuI, KHMDS, 1,10-phen, toluene, 90 °C (46%); (iv) TBAF, THF, −78 °C (40%).

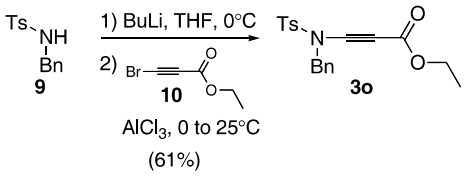
Our attention was then directed towards the synthesis of ynamides bearing an electron-withdrawing group at the acetylenic position. To date, no method to couple amides or sulfonamides with electron-deficient haloacetylenes has been published. Indeed, all our attempts to couple **2e** with ethyl 3-bromopropynoate **10** utilizing different copper-based coupling methodologies failed. Instead, **3n** was synthesized from **3l** in two steps (Scheme 2).

Electron-poor ynamide **3o** was also prepared. Unlike all previous cases, it was obtained through an unprecedented



Scheme 2. Synthesis of *N*-ethoxycarbonylethynyl-*N*-phenylcarbamic acid methyl ester **3n**.

conjugate addition/elimination process. Sulfonamide **9** was first deprotonated with butyllithium, and was then added to the bromoester **10** in presence of aluminium chloride, yielding to **3o** in 61% (Scheme 3). Intrigued by this expedient synthesis, we attempted to apply this methodology to the preparation of **3n** from the amide **2e**. Unfortunately, this methodology is thus far only applicable to sulfonamides.



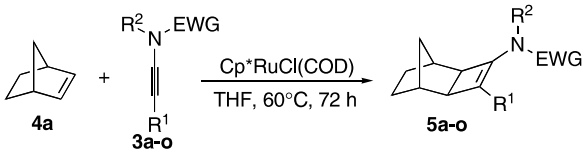
Scheme 3. Synthesis of **3o**.

2.2. Ruthenium-catalyzed [2+2] cycloadditions of ynamides

With these acyclic ynamides in hand, we studied their Ru-catalyzed [2+2] cycloadditions with norbornene **4a** and the results are shown in Table 2. Unlike alkynes with electron-withdrawing groups attached to the acetylenic carbon (e.g., COOEt[17a] or halides[17g]), which undergo Ru-catalyzed [2+2] cycloadditions with bicyclic alkenes at room temperature, ynamides were found to be less reactive and usually required an elevated temperature (60 °C) and a longer reaction time in order for the reaction to go to completion. Moderate to good yields of the Ru-catalyzed [2+2] cycloadditions were obtained with most of the ynamides. Interestingly, Hsung previously observed an unusual *endo* cycloaddition of ynamides with bicyclic alkenes in the Co-catalyzed [2+2+1] Pauson–Khand cycloadditions.[7e] We did not observe such an unusual change in stereochemistry with our Ru-catalyzed [2+2] cycloadditions with ynamides.[24] In all cases single stereoisomers, the *exo* cycloadducts **5** were formed.

Several trends were observed in the Ru-catalyzed [2+2] cycloadditions of acyclic ynamides (Table 2). With ynamides **3a–e** (R^1=Ph, entries 1–6), an increase in the steric bulk of the substituents (R^2 and EWG) on the nitrogen led to a decrease in the yield (compare entries 1 and 2, R^2=2° alkyl group vs 1° alkyl group; and compare entries 3 and 4, EWG=COOMe vs COO^{t}Bu). For ynamides **3e–h** (R^2=Ph, EWG=COOMe and R^1=aromatic groups, entries 6–9), both the electron-withdrawing aromatic group (*m*-F–C_6H_5, entry 9) and sterically bulky aromatic group (*o*-Me–C_6H_5, entry 8) led to a decrease in the yield in

Table 2. Ru-catalyzed [2+2] cycloaddition between norbornene and acyclic ynamides



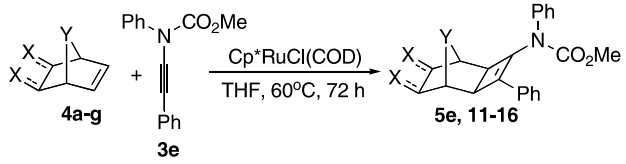
Entry	Ynamide	R^1	EWG	R^2	Yield (%)[a]
1	**3a**	Ph	COOMe	Cy	55[b]
2	**3b**	Ph	COOMe	CH_2CH_2Ph	73
3	**3c**	Ph	COOMe	CH_2Ph	91
4	**3d**	Ph	COO^{t}Bu	CH_2Ph	39 (5)
5		Ph	COO^{t}Bu	CH_2Ph	75 (9)[c]
6	**3e**	Ph	COOMe	Ph	97
7	**3f**	*p*-Me–C_6H_5	COOMe	Ph	85[b]
8	**3g**	*o*-Me–C_6H_5	COOMe	Ph	49 (32)[b]
9	**3h**	*m*-F–C_6H_5	COOMe	Ph	58[d]
10	**3i**	CH_2OH	COOMe	Ph	32[d]
11	**3j**	CH_2OTBS	COOMe	Ph	25[d]
12	**3k**	CH_2CH_2OTBS	COOMe	Ph	78
13	**3l**	$^i Pr_3Si$	COOMe	Ph	0 (93)
14	**3m**	H	COOMe	Ph	0[d]
15	**3n**	COOEt	COOMe	Ph	0 (34)[d]
16	**3o**	COOEt	SO_2Tol	Bn	0 (47)

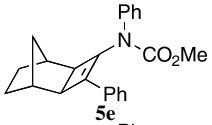
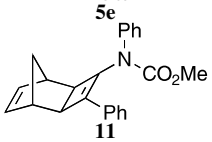
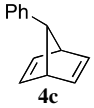
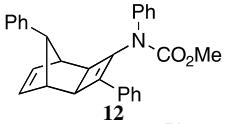
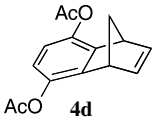
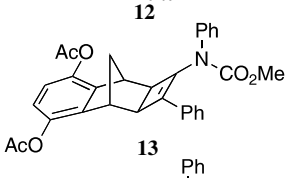
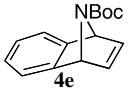
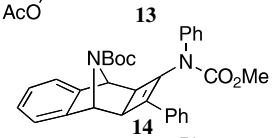
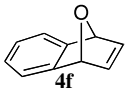
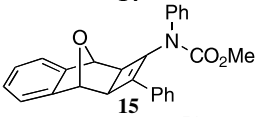
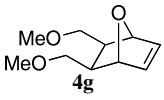
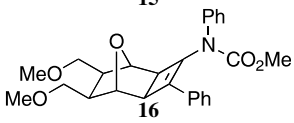
[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets.
[b] The reaction was stirred at 60 °C for 168 h.
[c] The reaction was stirred at 25 °C for 168 h.
[d] Polymeric materials were also obtained on the top of the column.

the cycloaddition. Ynamides containing propargylic alcohol and propargylic silyl ether groups (entries 10 and 11) gave low yields in the cycloadditions, which may be explained by the observance of polymeric materials. Terminal ynamide **3m** (R^1=H, entry 14) gave only polymeric materials under the cycloaddition conditions. Also, ynamide **3l**, with a very bulky group on the alkyne (R^1=Si^{i}Pr$_3$, entry 13) and ynamide **3n**, containing an electron-withdrawing group (R^1=COOEt, entry 15), were both inert in the Ru-catalyzed [2+2] cycloaddition. In the case of R^1 being an electron-withdrawing group, changing the electronics of the nitrogen (EWG=SO_2Tol, entry 16) did not improve the reactivity.

The scope of the reaction of ynamide **3e** with different bicyclic alkenes was also investigated (Table 3). In general, moderate to excellent yields were obtained (entries 1, 4–7), with the exception of norbornadienes **4b** and **4c** (entries 2 and 3). This was surprising since previous examples using these norbornadiene substrates suggested that the Ru-catalyzed [2+2] cycloaddition reaction was feasible with other alkynes.[17a–g] Furthermore, the presence of an extra double bond of the norbornadienes usually enhances the rate of the Ru-catalyzed [2+2] cycloaddition. In the present cases, we believe that the alkyne moiety of the ynamide fails to displace the alkene that chelates, in a bidentate fashion, to the ruthenium catalyst. Therefore, the relatively stable complex stays inert in the reaction conditions. As mentioned previously, higher temperature and longer reaction time are usually required with ynamides, which can be related to their lower affinity to complex to the ruthenium catalyst. Thus, utilizing **4d** (entry 4) as the alkene partner, where one of the double bonds is substituted by an aryl group,

Table 3. Ruthenium-catalyzed [2+2] cycloaddition bicyclic alkenes and ynamide **3e**



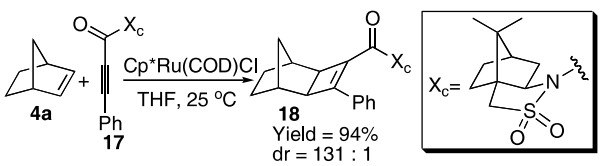
Entry	Alkene	Product	Yield (%)[a]
1	 **4a**	 **5e**	97
2	 **4b**	 **11**	0 (97)
3	 **4c**	 **12**	0 (98)
4	 **4d**	 **13**	90
5	 **4e**	 **14**	46
6	 **4f**	 **15**	83
7	 **4g**	 **16**	94

[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets.

the reaction proceeded smoothly and a 90% yield of the cycloadduct **13** was obtained. Similarly to **4d**, alkenes **4e**, **4f**, and **4g** containing a heteroatom-based group at the bridgehead position, also underwent cycloaddition with ynamide **3e** (entries 5–7).

2.3. Asymmetric ruthenium-catalyzed [2+2] cycloadditions of chiral ynamides

We have recently reported the first two examples of asymmetric induction studies of Ru-catalyzed [2+2] cycloadditions between an alkene and an alkyne using a chiral auxilliary attached to the alkyne component.[17d,e] With the excellent level of asymmetric induction obtained in the case of the chiral acetylenic acyl sultams

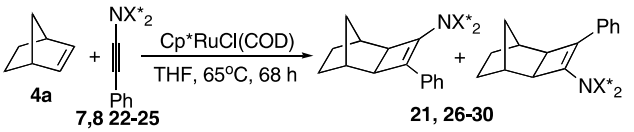


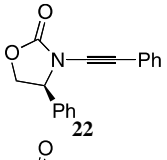
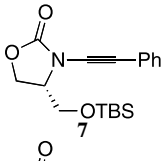
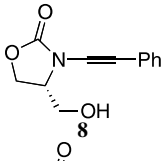
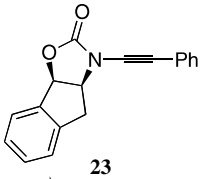
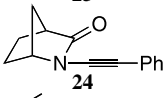
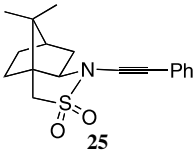
Scheme 4. Ru-catalyzed [2+2] cycloadditions between **4a** and **17**.

(Scheme 4) and good reactivity of acyclic ynamides in the Ru-catalyzed [2+2] cycloadditions, we decided to explore the chiral cyclic ynamides. Since the chiral functional group would be closer to the reaction center, a greater degree of asymmetric induction was anticipated. On the other hand, this could also mean increased steric congestion, which could potentially decrease the rate of the reaction or even suppress the formation of the cycloadduct since the acetylenic electron-withdrawing carbonyl group is not present anymore.

Several known (**22**, **23**) and new chiral cyclic ynamides (**7**, **8**, **24**, **25**) were synthesized and the results of the Ru-catalyzed [2+2] cycloadditions of these chiral cyclic ynamides are shown in Table 4. Good yields of the cycloadditions were obtained with chiral cyclic ynamides **7**, **8**, **22** and **23** (entries 1–5), however, the diastereoselectivity was only low to moderate. The diastereomeric ratios (dr) were determined by 400 MHz ^{1}H NMR and the peaks were compared to the 1:1 mixture of the diastereomers, which were synthesized using Buchwald's Cu-catalyzed amidation of vinyl iodide **19** (Scheme 5).[25]

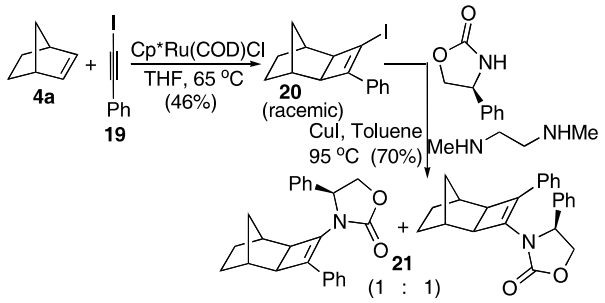
Table 4. Ru-catalyzed [2+2] cycloaddition between norbornene and chiral cyclic ynamides



Entry	Ynamide	Product (% yield)[a]	dr (%)[b]
1	 22	**21** (83)	72:28
2[c]	 7	**26** (72)	58:42
3[c]	 8	**27** (81)[d]	71:29
4	 23	**28** (82)	74:26
5[e]		**28** (60)[d]	75:25
6[c]	 24	**29** (0)[d]	NA
7	 25	**30** (0)[d]	NA

[a] Yield of isolated cycloadducts after column chromatography. Yield of recovered ynamide in brackets.
[b] Diastereomeric ratios (dr) measured by 400 MHz ^{1}H NMR.
[c] The reaction was stirred for 168 h.
[d] 16–94% of starting material recovered.
[e] The reaction was stirred at 25 °C for 216 h.

A decrease in the reaction temperature led to a corresponding decrease in the yield and no improvement of the diastereoselectivity was observed (entries 4 and 5). Ynamides attached to bicyclic frameworks were too bulky and were found to be inert in the Ru-catalyzed [2+2] cycloadditions (entries 6 and 7). It is worth noting that ynamide **25** was unreactive in the Ru-catalyzed [2+2] cycloaddition, but that amide **17** (Scheme 4), with an extra carbonyl group between the nitrogen atom and the acetylenic carbon, gave excellent yield and excellent diastereoselectivity in the cycloaddition.



Scheme 5. Synthesis of 1:1 diastereomers of **23**.

3. Conclusion

In summary, we have demonstrated that the ynamide moiety is compatible with the Ru-catalyzed [2+2] cycloadditions and that the reactivity of ynamide functionality is generally lower than other electron-deficient alkynes. We also found that diverse bicyclic alkenes could be utilized, with the exception of norbornadienes. Moderate to good yields of the cycloadditions were obtained with various acyclic and cyclic ynamides. However, only low to moderate levels of asymmetric induction was observed in the Ru-catalyzed [2+2] cycloadditions with chiral cyclic ynamides. Futher investigations on the mechanism of the cycloaddition, improvement of the asymmetric induction using other chiral ynamides, and the studies on regioselectivity of the Ru-catalyzed [2+2] cycloadditions between unsymmetrical bicyclic alkenes and ynamides are currently in progress in our laboratory.

4. Experimental

All reactions were carried out in an atmosphere of dry nitrogen at ambient temperature unless otherwise stated. Standard column chromatography was performed on 230–400 mesh silica gel (obtained from Silicycle) using flash column chromatography techniques.[26] Analytical thin-layer chromatography (TLC) was performed on Merck precoated silica gel 60 F_{254} plates. All glassware was flame dried under an inert atmosphere of dry nitrogen. Infrared spectra were taken on a Bomem MB-100 FTIR spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance-300, 400 or 600 spectrometer. Chemical shifts for ^{1}H NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent resonance as the internal standard (chloroform: δ 7.26 ppm). Chemical shifts for ^{13}C NMR spectra are reported in parts per million (ppm) from tetramethylsilane with the solvent as the internal standard (deuterochloroform: δ 77.0 ppm). High resolution mass spectra were done by McMaster Regional Centre for Mass Spectrometry at McMaster University, Hamilton, Ontario. Elemental analyses were performed by Canadian Microanalytical Service Ltd, British Columbia or by Quantitative Technologies Inc., New Jersey. Unless stated otherwise, commercial reagents were used without purification. Solvents were purified by distillation under dry nitrogen: from CaH_2 (pyridine); from sodium (toluene); and from potassium/benzophenone (THF). Ynamides **22** and **23**,[27] and Cp*RuCl(COD)[28] were prepared according to literature procedures.

Special note: for some of the acyclic ynamides as well as their corresponding [2+2] cycloadducts, some of the ^{13}C NMR signals (especially those of acetylenic, olefinic and carbonyl carbons, which are directly attached to the nitrogen) are severely broadened and virtually lost

(or very hard to detect) in 1-D ^{13}C NMR spectra. This is due to the system undergoing chemical exchange near the coalescence point, and in these cases, 2-D HMBC spectra were obtained in which the 'missing peaks' can be detected.[29]

4.1. Synthesis of ynamides

General procedure (A) for the synthesis of the ynamides. A mixture of the amide (1.0 equiv), alkynyl halide (2.0 equiv), copper iodide (0.2 equiv), 1,10-phenanthroline (0.25 equiv), and toluene (~0.6 M w.r.t. the amide) was prepared in an oven-dried round-bottomed flask, equipped with a condenser, under nitrogen. The mixture was heated at 90 °C and potassium bis(trimethylsilyl)amide (KHMDS, 1.2 equiv, 0.5 M in toluene) was added slowly via a syringe pump over 3–4 h. The reaction mixture was stirred at 90 °C for 12 h under nitrogen. The reaction mixture was diluted with diethyl ether and subsequently washed three times with 2:1 mixture of saturated sodium chloride solution and concentrated NH_4OH. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with saturated sodium chloride, dried over $MgSO_4$, filtered, and concentrated using rotary evaporation. The crude product was then purified by column chromatography (hexanes or ethyl acetate/hexanes mixture) using silica gel pre-treated with triethylamine.

General procedure (B) for the synthesis of the ynamides. To a cold solution (0 °C) of the amide (1.0 equiv) in pyridine (0.4 M) was added dropwise potassium bis(trimethylsilyl)-amide (KHMDS, 1 equiv, 0.5 M in toluene). The reaction was stirred for 15 min then a solution of copper iodide (1.0 equiv) in pyridine was added via a cannula. The resulting mixture was allowed to warm up to 25 °C and stirred for 2 h. A solution of alkynyl halide (2.0 equiv) in THF was added via cannula over 30 min and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with diethyl ether and washed three times with 2:1 mixture of saturated sodium chloride solution and concentrated NH_4OH. The aqueous layer was extracted three times with diethyl ether and the combined organic layers were washed with saturated sodium chloride, dried over $MgSO_4$, filtered, and concentrated using rotary evaporation. The crude product was then purified by column chromatography (hexanes or ethyl acetate/hexanes mixture) using silica gel treated with triethylamine.

General procedure (C) for the synthesis of the ynamides. To a cold solution (0 °C) of the sulfonamide (1.0 equiv) in THF (~0.4 M w.r.t. the amide) prepared in an oven-dried round-bottomed flask under nitrogen was added dropwise a solution of butyllithium in THF (2.5 M, 1.01 equiv). The mixture was stirred at 0 °C for 15 min and aluminium chloride (0.1 equiv) was added. The reaction mixture was then added via cannula to a cold solution (0 °C) of bromoalkyne (1.1 equiv) in THF (~0.8 M w.r.t. the bromoalkyne). The reaction mixture was stirred 30 min at 0 °C and then allowed to warm to room temperature until completion. The reaction mixture was quenched with water and diluted with diethyl ether, and the water was subsequently removed using Na_2SO_4. The organic layer was filtered, and concentrated using rotary evaporation. The crude product was then purified by column chromatography (ethyl acetate/hexanes mixture) using silica.

4.1.1. *N*-Cyclohexyl-*N*-phenylethynylcarbamic acid methyl ester (3a). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (298.9 mg, 1.651 mmol) and *N*-cyclohexylcarbamic acid methyl ester **2a** (127.4 mg, 0.8106 mmol), copper iodide (8.9 mg, 0.047 mmol), 1,10-phenanthroline (20.7 mg, 0.115 mmol), and KHMDS (0.5 M in toluene, 2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide **3a** (89.3 mg, 0.347 mmol, 43%) as a yellow oil. R_f 0.47 (EtOAc/hexanes=1:4); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.43 (m, 2H), 7.24–7.35 (m, 3H), 3.99 (br t, 1H, J=12.0 Hz), 3.84 (s, 3H), 1.82–1.89 (m, 4H), 1.58–1.68 (m, 3H), 1.33–1.43 (m, 2H), 1.11–1.19 (m, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 155.4, 131.1, 128.2, 127.4, 123.4, 80.6, 72.3, 56.5, 53.9, 30.5, 25.3, 25.1. This is a known compound and the spectral data are identical to those reported in the literature.[31]

4.1.2. *N*-Phenylethyl-*N*-phenylethynylcarbamic acid methyl ester (3b). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (662 mg, 3.657 mmol) and *N*-phenylcarbamic acid methyl ester **2b** (209.5 mg, 1.169 mmol), copper iodide (16.7 mg, 0.088 mmol), 1,10-phenanthroline (24.7 mg, 0.137 mmol), and KHMDS (2.8 mL, 1.4 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:99) to provide **3b** (171 mg, 0.6121 mmol, 52%) as an orange oil. R_f 0.43 (EtOAc/hexanes=1:9); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.47 (m, 10H), 3.87 (t, 2H, J=7.8 Hz), 3.84 (s, 3H), 3.09 (t, 2H, J=7.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 137.9, 131.3, 128.9, 128.5, 128.2, 127.6, 126.6, 123.1, 82.7, 71.0, 54.0, 51.3, 34.1. This is a known compound and the spectral data are identical to those reported in the literature.[2]

4.1.3. *N*-Benzyl-*N*-phenylethynylcarbamic acid methyl ester (3c). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (476 mg, 2.623 mmol) and *N*-benzylcarbamic acid methyl ester **2c** (208.7 mg, 1.263 mmol), copper iodide (47.6 mg, 0.250 mmol), 1,10-phenanthroline (59.8 mg, 0.332 mmol), and KHMDS (3.0 mL, 1.5 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide **3c** (205.7 mg, 0.7753 mmol, 61%) as a yellow oil. R_f 0.31 (EtOAc/hexanes=1:9); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.25–7.42 (m, 10H), 4.71 (s, 2H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.5, 135.8, 131.1, 128.5, 128.1, 128.0, 127.5, 123.0, 82.9, 71.1, 54.1. This is a known compound and the spectral data are identical to those reported in the literature.[32]

4.1.4. *N*-Phenyl-*N*-phenylethynylcarbamic acid methyl ester (3e). Following the above general procedure (A) with bromoethynylbenzene **1a**[30] (478.1 mg, 2.641 mmol) and *N*-phenylcarbamic acid methyl ester **2a** (209.2 mg, 1.384 mmol), copper iodide (57.3 mg, 0.301 mmol), 1,10-phenanthroline (60.9 mg, 0.338 mmol), and KHMDS (3.2 mL, 1.6 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to

provide **3e** (225.6 mg, 0.8978 mmol, 65%) as a yellow oil. R_f 0.32 (EtOAc/hexanes=1:9); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26–7.56 (m, 10H), 3.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 139.5, 131.4, 129.0, 128.2, 127.8, 127.0, 124.6, 122.8, 82.7, 70.1, 54.4. This is a known compound and the spectral data are identical to those reported in the literature.[33]

4.1.5. *N*-Phenyl-*N*-*p*-tolylethynylcarbamic acid methyl ester (3f). Following the above general procedure (A) with 1-bromoethynyl-4-methylbenzene **1b**[30] (596 mg, 3.040 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (231 mg, 1.528 mmol), copper iodide (64.2 mg, 0.337 mmol), 1,10-phenanthroline (74.9 mg, 0.416 mmol), and KHMDS (3.6 mL, 1.8 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3f** (196.1 mg, 0.7391 mmol, 48%) as an orange solid (mp 59–63 °C). R_f 0.39 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3045 (w), 2955 (w), 2252 (m), 1738 (s), 1595 (w), 1492 (m), 1439 (m), 1362 (m), 1289 (s), 1124 (w), 1052 (w), 738 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61–7.63 (m, 2H), 7.40–7.47 (m, 4H), 7.32 (m, 1H), 7.15–7.17 (m, 2H), 3.93 (s, 3H), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.6, 139.5, 137.7, 131.2, 128.9, 128.8, 126.7, 124.4, 119.5, 81.9, 70.0, 54.1, 21.2. HRMS calcd for $C_{17}H_{15}NO_2$: *m*/*z* 265.1103, found *m*/*z* 265.1113. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70. Found C, 76.80; H, 5.86.

4.1.6. *N*-Phenyl-*N*-*o*-tolylethynylcarbamic acid methyl ester (3g). Following the above general procedure (A) with 1-bromoethynyl-2-methylbenzene **1c**[17g] (321.4 mg, 1.648 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (129.6 mg, 0.8579 mmol), copper iodide (36.4 mg, 0.191 mmol), 1,10-phenanthroline (40.9 mg, 0.227 mmol), and KHMDS (2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3g** (89.5 mg, 0.337 mmol, 39%) as an orange oil. R_f 0.39 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2987 (w), 2305 (w), 2250 (w), 1738 (m), 1491 (w), 1439 (w), 1360 (w), 1266 (s), 896 (w), 739 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43–7.46 (m, 2H), 7.25–7.30 (m, 3H), 7.15 (m, 1H), 6.99–7.06 (m, 3H), 3.77 (s, 3H), 2.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.7, 139.5, 139.5, 131.1, 129.3, 128.9, 127.6, 126.9, 125.4, 124.4, 122.6, 86.6, 69.3, 54.3, 20.6. HRMS calcd for $C_{17}H_{15}NO_2$: *m*/*z* 265.1103, found *m*/*z* 265.1109.

4.1.7. *N*-(*m*-Fluorophenylethynyl)-*N*-phenylcarbamic acid methyl ester (3h). Following the above general procedure (A) with 1-bromoethynyl-3-fluorobenzene **1d**[17g] (335 mg, 1.683 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (133.7 mg, 0.8851 mmol), copper iodide (37.5 mg, 0.197 mmol), 1,10-phenanthroline (44.8 mg, 0.249 mmol), and KHMDS (2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:19) to provide **3h** (129.4 mg, 0.4805 mmol, 54%) as an orange solid (mp 26–27 °C). R_f 0.37 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3065 (w), 2955 (w), 2252 (s), 1738 (s), 1579 (m), 1490 (m), 1439 (m), 1363 (m), 1290 (s), 1053 (w), 940 (w), 738 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.80–7.39 (m, 9H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 162.3 (d, J=246.2 Hz), 154.5, 139.2, 129.7 (d, J=8.7 Hz), 129.0, 127.1, 127.0 (d, J=2.4 Hz), 124.7, 124.6, 117.9 (d, J=22.8 Hz), 114.9 (d, J=21.2 Hz), 83.7, 69.1 (d, J=3.0 Hz), 54.4. HRMS calcd for $C_{16}H_{12}NO_2F$: *m*/*z* 269.0852, found *m*/*z* 269.0845. Anal. Calcd for $C_{16}H_{12}NO_2F$: C, 71.37; H, 4.49. Found C, 71.48; H, 4.30.

4.1.8. *N*-(3-Hydroxy-1-propynyl)-*N*-phenylcarbamic acid methyl ester (3i). A solution of **3j** (79.4 mg, 0.249 mmol) in THF (0.5 mL) was cooled to −78 °C under nitrogen in a dry round-bottom flask. A solution of TBAF (1 M in THF, 0.46 mL, 0.46 mmol) was added dropwise and the resulting mixture was stirred for 1 h. The reaction was quenched with water at −20 °C and the aqueous layer was extracted with ethyl acetate three times. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified using flash chromatography (EtOAc/hexanes=2:3) to provide **3i** (33.4 mg, 0.163 mmol, 65%) as a white solid (mp 81–84 °C). R_f 0.48 (EtOAc/hexanes=2:3); IR (CH_2Cl_2, NaCl) 3052 (w), 2987 (w), 2305 (w), 2253 (w), 1740 (m), 1487 (w), 1442 (w), 1266 (s), 1016 (w), 888 (w), 739 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.45 (m, 4H), 7.28 (m, 1H), 4.43 (s, 2H), 3.85 (s, 3H), 2.11 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.0, 139.2, 129.0, 127.2, 124.8, 79.4, 68.6, 54.4, 51.1. HRMS calcd for $C_{11}H_{11}NO_3$: *m*/*z* 205.0739, found *m*/*z* 207.0745.

4.1.9. *N*-[3-(*tert*-Butyldimethylsilyloxy)-1-propynyl]-*N*-phenylcarbamic acid methyl ester (3j). Following the above general procedure (A) with (3-bromoprop-2-ynyloxy)-*tert*-butyldimethylsilane **1e**[34] (146.4 mg, 0.5874 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (120.6 mg, 0.7984 mmol), copper iodide (49.7 mg, 0.261 mmol), 1,10-phenanthroline (49.6 mg, 0.275 mmol), and KHMDS (2.0 mL, 1.0 mmol). The crude product was purified by column chromatography (Et_2O/pentane=1:9) to provide **3j** (51.4 mg, 0.161 mmol, 35%) as an orange oil. R_f 0.48 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 3054 (w), 2987 (w), 2955 (w), 2859 (w), 2305 (w), 2253 (w), 1739 (m), 1596 (w), 1440 (w), 1266 (s), 1075 (w), 896 (w), 735 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44–7.46 (m, 2H), 7.35–7.41 (m, 2H), 7.26 (m, 1H), 4.49 (s, 2H), 3.86 (s, 3H), 0.91 (s, 9H), 0.12 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.9, 139.3, 128.8, 127.0, 124.6, 78.4, 68.9, 54.1, 51.8, 25.8, 18.2, −5.2. HRMS calcd for $C_{17}H_{25}NO_3Si$: *m*/*z* 319.1604, found *m*/*z* 319.1611.

4.1.10. *N*-[4-(*tert*-Butyldimethylsilyloxy)-1-butynyl]-*N*-phenylcarbamic acid methyl ester (3k). Following the above general procedure (A) with **1f**[17g] (156.1 mg, 0.5930 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (66.1 mg, 0.438 mmol), copper iodide (20.8 mg, 0.109 mmol), 1,10-phenanthroline (18.4 mg, 0.102 mmol), and KHMDS (0.75 mL, 0.38 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3k** (37.8 mg, 0.113 mmol, 26%) as a yellow oil. R_f 0.38 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2956 (w), 2930 (w), 2857 (w), 1737 (m), 1492 (w), 1440 (m), 1298 (m), 1266 (s), 1104 (w), 838 (w), 740 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (m, 2H), 7.30 (m, 2H), 7.19 (m, 1H), 3.78 (s, 3H), 3.67 (t, 2H, J=7.0 Hz), 2.48 (t, 2H, J=7.0 Hz), 0.81 (s, 9H), −0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.2, 139.8, 128.8, 126.7,

124.6, 74.6, 66.8, 62.0, 54.1, 25.8, 22.9, 18.3, −5.3. HRMS calcd for $C_{18}H_{27}NO_3Si$: *m/z* 333.1760, found *m/z* 333.1752.

4.1.11. *N*-Phenyl-*N*-triisopropylsilylethynylcarbamic acid methyl ester (3l). Following the above general procedure (A) with bromoethynyltriisopropylsilane **1g**[35] (2.9332 g, 11.226 mmol) and *N*-phenylcarbamic acid methyl ester **2e** (1.4324 g, 9.4823 mmol), copper iodide (0.5808 g, 3.050 mmol), 1,10-phenanthroline (615.7 mg, 3.417 mmol), and KHMDS (24.0 mL, 12.0 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide **3l** (2.8186 g, 8.5017 mmol, 90%) as a yellow oil. R_f 0.53 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3052 (w), 2949 (m), 2865 (m), 2305 (w), 2178 (m), 1740 (m), 1596 (w), 1492 (w), 1440 (m), 1266 (s), 1055 (w), 881 (w), 740 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.56 (m, 2H), 7.41 (m, 2H), 7.29 (m, 1H), 3.90 (s, 3H), 1.14 (s, 21H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 139.2, 128.7, 126.5, 123.9, 96.2, 68.9, 54.0, 18.5, 11.3. HRMS calcd for $C_{19}H_{29}NO_2Si$: *m/z* 331.1968, found *m/z* 331.1977. Anal. Calcd for $C_{19}H_{29}NO_2Si$: C, 68.83; H, 8.82. Found C, 68.72; H, 8.99.

4.1.12. *N*-Ethynyl-*N*-phenylcarbamic acid methyl ester (3m). A solution of **3l** (2.6024 g, 7.8497 mmol) in THF (15 mL) was cooled to −78 °C under nitrogen in a dry round-bottom flask. A solution of TBAF (1 M in THF, 15.0 mL, 15.0 mmol) was added dropwise and the resulting mixture was stirred for 1 h. The reaction was quenched with water at −20 °C and the aqueous layer was extracted with ethyl acetate three times. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified using flash chromatography (EtOAc/hexanes=1:24) to provide **3m** (1.0451 g, 5.9658 mmol, 76%) as a white solid (mp 48–50 °C). R_f 0.38 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3312 (w), 3055 (w), 2987 (w), 2306 (w), 2148 (w), 1742 (w), 1493 (w), 1440 (w), 1299 (w), 1266 (s), 896 (w), 738 (s), 705 (m); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.47 (m, 2H), 7.34 (m, 2H), 7.29 (m, 1H), 3.89 (s, 3H), 2.92 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 138.8, 129.0, 127.2, 124.6, 76.2, 58.5, 54.4. HRMS calcd for $C_{10}H_9NO_2$: *m/z* 175.0633, found *m/z* 175.0631.

4.1.13. *N*-Ethoxycarbonylethynyl-*N*-phenylcarbamic acid methyl ester (3n). In a dry round-bottom flask, at −78 °C and under a flow of nitrogen, LiHMDS (1 M in THF, 1.85 mL, 1.85 mmol) was added dropwise to a solution of **3m** (186.4 mg, 1.064 mmol) in THF (8.5 mL). The reaction mixture was allowed to warm slowly to −40 °C and then stirred for 1 h. The reaction mixture was then added to a solution of ethyl chloroformate (0.165 mL, 1.73 mmol) in THF (2.9 mL) at −40 °C via a cannula. The reaction was quenched with a saturated NH_4Cl solution and the aqueous layer was extracted three times with ethyl acetate. The organic layers were combined, dried over $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified using flash chromatography (EtOAc/hexanes=1:9) to provide **3n** (29.1 mg, 0.118 mmol, 11%) as a white solid (mp 82–84 °C). R_f 0.36 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 3056 (w), 2981 (w), 2955 (w), 2237 (s), 1754 (s), 1705 (s), 1595 (w), 1492 (w), 1440 (m), 1288 (m), 1266 (s), 1197 (m), 1158 (m), 1025 (w), 896 (w), 740 (s); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39–7.45 (m, 4H), 7.34 (m, 1H), 4.24 (q, 2H, J=7.1 Hz), 3.93 (s, 3H), 1.30 (t, 3H, J=7.1 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.2, 154.0, 137.7, 129.3, 128.1, 125.0, 81.4, 65.8, 61.7, 55.0, 14.1. HRMS calcd for $C_{13}H_{13}NO_4$: *m/z* 247.0845, found *m/z* 247.0852.

4.1.14. Ethyl [benzyl-(toluene-4-sulfonyl)-amino]-propynoate (3o). Following the above general procedure (C) with sulfonamide **9** (204.1 mg, 0.781 mmol), THF (2.0 mL), BuLi (0.37 mL, 0.93 mmol), $AlCl_3$ (11.1 mg, 0.0832 mmol), alkynyl bromide **10**[36] (190.3 mg, 1.075 mmol) and THF (1.0 mL). The reaction mixture was stirred at 25 °C for 1.5 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes=1:19–3:7) to provide ynamide **3o** (171.0 mg, 0.4784 mmol, 61%) as a colorless oil. R_f 0.26 (EtOAc/hexanes=3:7); IR (CH_2Cl_2, NaCl) 3090 (w), 3066 (w), 3034 (w), 2983 (m), 2937 (m), 2219 (vs), 1704 (vs), 1374 (vs), 1165 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73 (d, 2H, J=8.4 Hz), 7.27–7.34 (m, 7H), 4.63 (s, 2H), 4.19 (q, 2H, J=7.1 Hz), 2.45 (s, 3H), 1.29 (t, 3H, J=7.1 Hz); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 153.9, 145.4, 134.2, 133.5, 129.8, 128.6, 127.7, 82.6, 68.0, 61.5, 55.4, 21.6, 14.1. HRMS (EI) calcd for $C_{19}H_{19}NO_4S$ (M^+): 357.1035; found: 357.1039.

4.1.15. (*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)oxazolidin-2-one (6). To a solution of (*S*)-4-hydroxymethyloxazolidin-2-one **5**[23] (1.16 g, 9.91 mmol) in CH_2Cl_2 (15 mL) were successively added triethylamine (1.50 mL, 10.8 mmol), 4-(*N*,*N*-dimethylamino)pyridine (DMAP, 70.3 mg, 0.575 mmol) and *tert*-butyl(chloro)dimethylsilane (TBSCl, 2.04 g, 13.5 mmol). The reaction mixture was stirred for 16 h at 25 °C under N_2 then quenched with of water (1 mL). Magnesium sulfate was added and the mixture was filtered, and the filtrate was concentrated to dryness. The crude product was purified by column chromatography (EtOAc/hexanes=3:2) to give the product **6** (1.84 g, 7.95 mmol, 80%) as a semi-solid. $[\alpha]_D^{23}$ +26 (*c* 0.59, CH_2Cl_2); R_f 0.55 (EtOAc); IR (neat) 3327 (s), 2956 (s), 2936 (s), 1748 (s), 1253 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.30 (br s, 1H), 4.42 (app t, 1H, J=8.6 Hz), 4.18 (dd, 1H, J=8.7, 4.8 Hz), 3.89–3.92 (m, 1H), 3.59 (d, 2H, J=5.4 Hz), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 160.0, 67.1, 64.6, 53.6, 25.7, 18.1, −5.6. HRMS (*m/z*) for $C_{10}H_{21}NO_3Si$ calcd 231.1291, found 231.1299.

4.1.16. (*S*)-4-(*tert*-Butyldimethylsilyloxymethyl)-3-phenylethnyloxazolidin-2-one (7). Following the above general procedure (A) with alkynyl bromide **1a** (1.095 g, 6.049 mmol) and **6** (900.3 mg, 3.891 mmol), copper iodide (303.3 mg, 1.593 mmol), 1,10-phenanthroline (295.7 mg, 1.641 mmol), and KHMDS (0.5 M in toluene, 12.4 mL, 6.2 mmol). The crude product was purified by column chromatography (EtOAc/hexanes=1:4) to give the ynamide **7** (592.6 mg, 1.788 mmol, 46%) as a semi-solid. $[\alpha]_D^{23}$ −94 (*c* 0.30, CH_2Cl_2); R_f 0.56 (EtOAc/hexanes=2:3); IR (neat) 2961 (m), 2937 (m), 2251 (m), 1777 (s), 1414 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (m, 2H), 7.30 (m, 3H), 4.48 (app t, 1H, J=8.6 Hz), 4.43 (dd, 1H, J=8.5, 5.2 Hz), 4.10–4.13 (m, 1H), 4.04 (dd, 1H, J=11.3, 3.0 Hz), 3.72 (d, 1H, J=11.3 Hz), 0.89

(s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 155.8, 131.6, 128.2, 128.1, 122.1, 77.8, 72.2, 65.4, 60.5, 58.6, 25.6, 18.0, −5.6. HRMS (*m/z*) for $C_{18}H_{25}NO_3Si$ calcd 331.1604, found 331.1620.

4.1.17. (*S*)-4-Hydroxymethyl-3-phenylethynyl-oxazolidin-2-one (8). To a cold solution (−78 °C) of **7** (500.1 mg, 1.508 mmol) in THF (3 mL) under N_2 was slowly added a solution of tetrabutylammonium fluoride (1 M in THF, 3.0 mL, 3.0 mmol). After 30 min, the reaction was quenched with saturated NH_4Cl solution (3 mL) and diluted with EtOAc. Layers were separated and aqueous layer was extracted three times with EtOAc. Organics were combined, dried over sodium sulfate and concentrated. The crude product was purified by column chromatography (EtOAc/hexanes=2:3) to give ynamide **8** (142.3 mg, 0.6551 mmol, 48%) as a solid (mp 109–112 °C). $[\alpha]_D^{23}$ −63 (*c* 0.40, CH_2Cl_2); R_f 0.13 (EtOAc/hexanes=2:3); IR (neat) 2942 (w), 2978 (w), 2253 (m), 1753 (s), 1414 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42–7.26 (m, 2H), 7.29–7.33 (m, 3H), 4.46–4.56 (m, 2H), 4.16–4.22 (m, 1H), 4.11 (dd, 1H, *J*=12.2, 3.5 Hz), 3.81 (d, 1H, *J*=11.8 Hz), 2.06 (br s, 1H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 156.1, 131.5, 128.3, 121.9, 77.4, 72.5, 65.5, 60.1, 58.6. HRMS (*m/z*) for $C_{12}H_{11}NO_3$ calcd 217.0739, found 217.0729.

4.1.18. (+)-3-Phenylethynyl-3,3a,8,8a-tetrahydroindeno[1,2-*d*]oxazol-2-one (24). Following the above general procedure (B) with bromoethynylbenzene **1a** (631.2 mg, 3.487 mmol) and (+)-2-azabicyclo[2.2.1]heptan-3-one[37] (199.3 mg, 1.861 mmol), copper iodide (354.1 mg, 1.859 mmol), and KHMDS (0.5 M in toluene, 3.6 mL, 1.8 mmol). The crude mixture was the purified by column chromatography (EtOAc/hexanes=1:4) affording the ynamide **24** (181.9 mg, 0.8615 mmol, 46%) as a solid (mp 73–77 °C). $[\alpha]_D^{23}$ +52 (*c* 0.37, CH_2Cl_2); R_f 0.45 (EtOAc/hexanes=3:7); IR (neat) 3052 (w), 2987 (w), 2246 (m), 1727 (s), 1397 (s), 1266 (vs) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.40 (m, 2H), 7.20–7.27 (m, 3H), 4.15 (br s, 1H), 2.85 (m, 1H), 2.03 (dm, 1H, *J*=9.9 Hz), 1.81–1.97 (m, 3H), 1.67–1.74 (m, 1H), 1.47 (dm, 1H, *J*=9.9 Hz); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 177.7, 131.2, 128.1, 127.6, 122.7, 79.4, 72.2, 64.4, 44.1, 39.0, 27.6, 24.1. HRMS (*m/z*) for $C_{14}H_{13}NO$ calcd 211.0997, found 211.0991. Anal. Calcd for $C_{14}H_{13}NO$=C, 79.59%; H, 6.20%; found C, 79.70%; H, 6.08%.

4.1.19. (−)-10,10-Dimethyl-4-phenylethynyl-3-thia-4-aza-tricyclo[5.2.1.0^{1,5}]decane-3,3-dioxide (25). Following the above general procedure (B) with bromoethynylbenzene **1a** (69.4 mg, 0.383 mmol) and (1*S*)-(−)-2,10-camphorsultam (41.1 mg, 0.191 mmol), copper iodide (37.4 mg, 0.196 mmol), and KHMDS (0.5 M in toluene, 0.38 mL, 0.19 mmol). The crude mixture was the purified by column chromatography (EtOAc/hexanes=1:4) affording the ynamide **10f** (41.5 mg, 0.132 mmol, 69%) as a pale yellow oil. $[\alpha]_D^{23}$ −146 (*c* 0.52, CH_2Cl_2); R_f 0.41 (EtOAc/hexanes=3:7); IR (neat) 3058 (w), 3000 (m), 2962 (s), 2237 (s), 1336 (s), 1146 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40–7.44 (m, 2H), 7.27–7.29 (m, 3H), 3.68 (dd, 1H, *J*=8.1, 4.1 Hz), 3.29 (s, 2H), 2.29 (dd, 1H, *J*=13.4, 3.0 Hz), 1.98 (m, 1H), 1.89–1.93 (m, 2H), 1.82 (dd, 1H, *J*=13.4, 8.2 Hz), 1.43–1.46 (m, 1H), 1.33–1.36 (m, 1H), 1.15 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 131.7, 128.1, 127.8, 122.6, 76.7, 72.6, 67.2, 51.2, 49.8, 48.0, 44.4, 34.4, 31.6, 27.0, 20.2, 19.9. HRMS (*m/z*) for $C_{18}H_{21}NO_2S$ calcd 315.1293, found 315.1273. Anal. Calcd for $C_{18}H_{21}NO_2S$=C, 68.54%; H, 6.71%; found C, 68.79%; H, 6.66%.

4.2. Ruthenium-catalyzed [2+2] cycloaddition

General procedure (D) for the Ru-catalyzed [2+2] cycloaddition between bicyclic alkenes and ynamides. A mixture of bicyclic alkene (2.5–5 equiv), ynamide (1 equiv) and THF (0.2–0.5 M w.r.t. the ynamide) in an oven-dried vial was added via a cannula to an oven-dried screw-cap vial containing Cp*RuCl(COD) (weighed out from a dry box, 5–10 mol%) under nitrogen. The reaction mixture was stirred in the dark at 25 or 65 °C for 68–168 h. The crude product was purified by column chromatography to give the cycloadduct.

4.2.1. Cycloadduct 5a. Following the above general procedure (D) with norbornene **4a** (15.8 mg, 0.168 mmol), ynamide **3a** (16.6 mg, 0.0645 mmol), THF (0.3 mL), and Cp*RuCl(COD) (6.2 mg, 0.016 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5a** (12.4 mg, 0.0354 mmol, 55%) as a slightly yellow oil. R_f 0.48 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3052 (m), 2987 (w), 2942 (w), 2305 (w), 1693 (m), 1442 (m), 1422 (m), 1266 (s), 894 (w), 740 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.28–7.29 (m, 4H), 7.20 (m, 1H), 3.93 (m, 1H), 3.59 (s, 3H), 2.74 (d, 1H, *J*=3.5 Hz), 2.60 (d, 1H, *J*=3.5 Hz), 2.30 (br s, 1H), 2.09 (br s, 1H), 1.90 (m, 1H), 1.72–1.82 (m, 4H), 1.51–1.66 (m, 5H), 1.26–1.37 (m, 2H), 1.06–1.19 (m, 3H), 0.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.7, 136.8, 133.7, 131.3, 128.1, 127.3, 126.4, 57.4, 52.7, 52.4, 43.9, 35.2, 34.2, 32.0, 31.1, 30.8, 28.6, 28.4, 26.0, 25.9, 25.5. HRMS calcd for $C_{23}H_{29}NO_2$: *m/z* 351.2198, found *m/z* 351.2189.

4.2.2. Cycloadduct 5b. Following the above general procedure (D) with norbornene **4a** (43.4 mg, 0.461 mmol), ynamide **3b** (26.9 mg, 0.0963 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.5 mg, 0.012 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5b** (26.1 mg, 0.0698 mmol, 73%) as a yellow oil. R_f 0.34 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 2950 (w), 2865 (w), 1711 (m), 1648 (w), 1493 (w), 1447 (m), 1390 (w), 1313 (w), 1203 (w), 765 (w), 694 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.34 (m, 10H), 3.80 (m, 1H), 3.68 (s, 3H), 3.60 (m, 1H), 2.83–2.99 (m, 2H), 2.74 (br s, 1H), 2.59 (d, 1H, *J*=3.2 Hz), 2.32 (s, 1H), 2.14 (br s, 1H), 1.61–1.70 (m, 3H), 1.07–1.22 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.1, 138.6, 134.1, 132.3, 130.7, 128.8, 128.4, 128.0, 126.9, 126.3, 52.6, 50.0, 48.6, 44.0, 35.4, 35.2, 34.5, 30.6, 28.4, 28.2. HRMS calcd for $C_{25}H_{27}NO_2$: *m/z* 373.2042, found *m/z* 373.2051.

4.2.3. Cycloadduct 5c. Following the above general procedure (D) with norbornene **4a** (31.7 mg, 0.337 mmol), ynamide **3c** (31.9 mg, 0.120 mmol), THF (0.3 mL), and

Cp*RuCl(COD) (4.9 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5c** (39.4 mg, 0.110 mmol, 91%) as an orange solid (mp 55–60 °C). R_f 0.34 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2953 (m), 2871 (w), 2305 (w), 1710 (s), 1648 (m), 1494 (w), 1447 (m), 1265 (s), 974 (w), 896 (w), 738 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.33 (m, 10H), 4.83 (d, 1H, J=15.3 Hz), 4.62 (d, 1H, J=15.4 Hz), 3.70 (s, 3H), 2.71 (br s, 1H), 2.54 (d, 1H, J=3.4 Hz), 2.26 (s, 1H), 2.00 (br s, 1H), 1.53–1.64 (m, 2H), 1.40 (m, 1H), 1.06–1.17 (m, 2H), 0.91 (m, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 155.6, 138.1, 134.3, 132.2, 130.5, 128.3, 128.0, 127.4, 127.2, 126.9, 52.9, 50.1, 50.0, 44.1, 35.2, 34.4, 30.4, 28.4, 28.1. HRMS calcd for $C_{24}H_{25}NO_2$: m/z 359.1885, found m/z 359.1892.

4.2.4. Cycloadduct 5d. Following the above general procedure (D) with norbornene **4a** (72.6 mg, 0.771 mmol), ynamide **3c** (32.5 mg, 0.106 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.3 mg, 0.011 mmol). The reaction mixture was stirred in the dark at 25 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5d** (31.8 mg, 0.0792 mmol, 75%) as a colorless oil. R_f 0.63 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 2949 (m), 2865 (w), 1698 (s), 1383 (m), 1364 (m), 1313 (m), 1248 (w), 1161 (m), 688 (w) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.13–7.25 (m, 10H), 4.79 (d, 1H, J=15.0 Hz), 4.46 (d, 1H, J=15.4 Hz), 2.68 (br s, 1H), 2.43 (br s, 1H), 2.23 (br s, 1H), 1.93 (br s, 1H), 1.50–1.54 (m, 2H), 1.36 (d, 1H, J=10.1 Hz), 1.28 (s, 9H), 1.02–1.08 (m, 2H), 0.84 (d, 1H, J=10.1 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.8, 138.7, 135.0, 132.6, 129.6, 128.3, 127.8, 127.3, 127.0, 126.6, 80.9, 50.2, 49.4, 44.3, 35.6, 34.3, 30.4, 28.5, 28.2, 28.1. HRMS calcd for $C_{27}H_{31}NO_2$: m/z 401.2355, found m/z 401.2330. Anal. Calcd for $C_{27}H_{31}NO_2$: C, 80.76; H, 7.78. Found C, 80.65; H, 7.89.

4.2.5. Cycloadduct 5e. Following the above general procedure (D) with norbornene **4a** (36.6 mg, 0.389 mmol), ynamide **3e** (32.5 mg, 0.129 mmol), THF (0.3 mL), and Cp*RuCl(COD) (5.2 mg, 0.014 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:49) to provide cycloadduct **5e** (43.3 mg, 0.125 mmol, 97%) as a pale yellow solid (mp 66–69 °C). R_f 0.36 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (w), 2955 (w), 2865 (w), 2363 (w), 2305 (w), 1715 (m), 1596 (w), 1493 (w), 1442 (w), 1266 (s), 894 (w), 741 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.18–7.38 (m, 10H), 3.73 (s, 3H), 2.70 (d, 1H, J=3.4 Hz), 2.64 (d, 1H, J=3.5 Hz), 2.35 (d, 1H, J=3.6 Hz), 1.95 (d, 1H, J=3.5 Hz), 1.55–1.73 (m, 2H), 0.92–1.30 (m, 4H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 158.0, 154.4, 139.6, 133.6, 131.7, 128.9, 127.9, 127.0, 126.8, 126.7, 126.6, 53.0, 49.8, 44.0, 35.5, 34.3, 30.8, 28.4, 28.2. HRMS calcd for $C_{23}H_{23}NO_2$: m/z 345.1729, found m/z 345.1722.

4.2.6. Cycloadduct 5f. Following the above general procedure (D) with norbornene **4a** (60.2 mg, 0.639 mmol), ynamide **3f** (41.5 mg, 0.156 mmol), THF (0.3 mL), and Cp*RuCl(COD) (8.7 mg, 0.023 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:24) to provide cycloadduct **5f** (48.0 mg, 0.134 mmol, 85%) as a yellow solid (mp 69–75 °C). R_f 0.36 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3052 (m), 2954 (m), 2871 (m), 2350 (w), 2298 (w), 1714 (s), 1597 (m), 1492 (m), 1440 (m), 1266 (s), 1062 (m), 894 (w), 734 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.31 (m, 4H), 7.18 (m, 1H), 6.99–7.06 (m, 4H), 3.65 (s, 3H), 2.59 (d, 1H, J=3.5 Hz), 2.54 (d, 1H, J=3.6 Hz), 2.26 (s, 3H), 2.25 (br s, 1H), 1.84 (d, 1H, J=3.6 Hz), 1.43–1.65 (m, 3H), 0.94–1.13 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 139.8, 136.9, 132.0, 130.8, 130.6, 128.9, 128.7, 126.7, 126.5, 53.0, 49.7, 43.8, 35.4, 34.3, 30.8, 28.5, 28.2, 21.3. HRMS calcd for $C_{24}H_{25}NO_2$: m/z 359.1885, found m/z 359.1896.

4.2.7. Cycloadduct 5g. Following the above general procedure (D) with norbornene **4a** (38.7 mg, 0.411 mmol), ynamide **3g** (38.6 mg, 0.146 mmol), THF (0.3 mL), and Cp*RuCl(COD) (6.3 mg, 0.017 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:9) to provide cycloadduct **5g** (26.7 mg, 0.0742 mmol, 51%) as pale yellow oil. R_f 0.53 (EtOAc/hexanes=1:4); IR (CH_2Cl_2, NaCl) 3054 (m), 2954 (m), 1718 (m), 1597 (w), 1491 (w), 1440 (m), 1348 (m), 1266 (s), 896 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.21–7.25 (m, 2H), 7.13–7.18 (m, 3H), 6.99–7.04 (m, 4H), 3.48 (s, 3H), 2.70 (d, 1H, J=3.0 Hz), 2.60 (d, 1H, J=3.4 Hz), 2.25 (s, 3H), 2.17 (br s, 1H), 1.85 (br s, 1H), 1.74 (d, 1H, J=10.1 Hz), 1.48–1.56 (m, 2H), 1.00–1.07 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.4, 139.0, 136.0, 135.4, 132.9, 129.6, 128.6, 127.7, 127.6, 127.0, 126.5, 124.8, 52.7, 49.7, 46.9, 35.6, 34.9, 30.6, 28.2, 28.1, 20.5. HRMS calcd for $C_{24}H_{25}NO_2$: m/z 359.1885, found m/z 359.1880.

4.2.8. Cycloadduct 5h. Following the above general procedure (D) with norbornene **4a** (35.0 mg, 0.372 mmol), ynamide **3h** (31.0 mg, 0.115 mmol), THF (0.3 mL), and Cp*RuCl(COD) (5.6 mg, 0.015 mmol). The reaction mixture was stirred in the dark at 60 °C for 168 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:19) to provide cycloadduct **5h** (24.3 mg, 0.0668 mmol, 58%) as a yellow oil. R_f 0.38 (EtOAc/hexanes=1:9); IR (CH_2Cl_2, NaCl) 3054 (m), 2954 (m), 2872 (w), 2298 (w), 1718 (m), 1610 (w), 1596 (w), 1581 (w), 1494 (w), 1440 (m), 1348 (m), 1266 (s), 1062 (w), 851 (w), 739 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.24–7.28 (m, 2H), 7.14–7.20 (m, 3H), 7.07 (m, 1H), 6.66–6.82 (m, 3H), 3.64 (s, 3H), 2.63 (d, 1H, J=3.6 Hz), 2.50 (d, 1H, J=3.6 Hz), 2.22 (d, 1H, J=3.5 Hz), 1.86 (d, 1H, J=3.4 Hz), 1.47–1.59 (m, 3H), 0.96–1.10 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 162.5 (d, J=244.8 Hz), 154.1, 139.4, 135.8 (d, J=7.2 Hz), 133.1, 129.2 (d, J=7.4 Hz), 129.0, 128.8, 127.0, 126.9, 122.4, 113.6 (d, J=21.4 Hz), 113.4 (d, J=21.7 Hz), 53.1, 50.0, 44.2, 35.5, 34.3, 30.7, 28.4, 28.2. HRMS calcd for $C_{23}H_{22}NO_2F$: m/z 363.1635, found m/z 363.1643.

4.2.9. Cycloadduct 5i. Following the above general procedure (D) with norbornene **4a** (44.6 mg, 0.474 mmol), ynamide **3i** (24.5 mg, 0.119 mmol), THF (0.3 mL), and

Cp*RuCl(COD) (7.3 mg, 0.019 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:4) to provide cycloadduct **5i** (11.6 mg, 0.0387 mmol, 32%) as a yellow oil. R_f 0.35 (EtOAc/hexanes = 2:3); IR (CH_2Cl_2, NaCl) 3052 (m), 2955 (m), 2871 (w), 1712 (m), 1596 (w), 1493 (w), 1442 (m), 1313 (m), 1266 (s), 1055 (w), 894 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.32–7.42 (m, 3H), 7.20–7.22 (m, 2H), 3.74 (m, 1H), 3.70 (s, 3H), 3.66 (m, 1H), 2.50 (br s, 1H), 2.27 (d, 1H, J = 3.3 Hz), 2.08 (d, 1H, J = 3.3 Hz), 1.77 (br s, 1H), 1.43–1.52 (m, 3H), 0.07–1.04 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.6, 139.2, 132.9, 129.2, 128.0, 127.9, 125.4, 57.6, 53.3, 49.3, 44.2, 35.0, 34.1, 30.3, 28.1, 27.9. HRMS calcd for $C_{18}H_{21}NO_3$: *m/z* 299.1521, found *m/z* 299.1530.

4.2.10. Cycloadduct 5j. Following the above general procedure (D) with norbornene **4a** (24.8 mg, 0.263 mmol), ynamide **3j** (21.0 mg, 0.0657 mmol), THF (0.3 mL), and Cp*RuCl(COD) (5.9 mg, 0.016 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:9) to provide cycloadduct **5j** (6.8 mg, 0.016 mmol, 25%) as a yellow oil. R_f 0.58 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2, NaCl) 3052 (w), 2981 (w), 2949 (w), 2305 (w), 1719 (w), 1442 (w), 1422 (w), 1266 (s), 1036 (w), 894 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37–7.40 (m, 2H), 7.33 (m, 1H), 7.20–7.22 (m, 2H), 3.70 (s, 3H), 3.48 (d, 1H, J = 13.6 Hz), 3.38 (d, 1H, J = 13.6 Hz), 2.73 (br s, 1H), 2.29 (d, 1H, J = 3.1 Hz), 2.07 (br s, 1H), 2.02 (br s, 1H), 1.51–1.53 (m, 3H), 0.96–1.04 (m, 3H), 0.81 (s, 9H), −0.07 (s, 3H), −0.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.1, 139.8, 132.3, 130.5, 129.2, 128.1, 127.6, 57.4, 52.9, 49.7, 44.2, 35.3, 34.4, 30.4, 28.1, 28.1, 25.9, 18.3, −5.4. HRMS calcd for $C_{24}H_{35}NO_3Si$: *m/z* 413.2386, found *m/z* 413.2391.

4.2.11. Cycloadduct 5k. Following the above general procedure (D) with norbornene **4a** (36.0 mg, 0.382 mmol), ynamide **3k** (37.8 mg, 0.113 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.9 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:24) to provide cycloadduct **5k** (37.7 mg, 0.0881 mmol, 78%) as a yellow oil. R_f 0.48 (EtOAc/hexanes = 1:9); IR (CH_2Cl_2, NaCl) 3052 (w), 2954 (m), 2871 (w), 1716 (m), 1442 (m), 1351 (w), 1266 (s), 1087 (w), 1055 (w), 836 (w), 740 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.36–7.39 (m, 2H), 7.29 (m, 1H), 7.21–7.22 (m, 2H), 3.70 (s, 3H), 3.43 (t, 2H, J = 7.2 Hz), 2.75 (br s, 1H), 2.18 (d, 1H, J = 3.1 Hz), 2.00 (br s, 1H), 1.98 (br s, 1H), 1.48–1.73 (m, 5H), 0.95–1.05 (m, 3H), 0.84 (s, 9H), −0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 154.2, 140.0, 133.4, 129.0, 128.0, 127.3, 125.1, 61.1, 52.8, 50.2, 45.4, 35.1, 34.1, 30.4, 30.4, 28.2, 28.0, 25.9, 18.2, −5.3. HRMS calcd for $C_{25}H_{37}NO_3Si$: *m/z* 427.2543, found *m/z* 427.2548.

4.2.12. Cycloadduct 13. Following the above general procedure (D) with alkene **4d** (73.6 mg, 0.285 mmol), ynamide **3e** (29.9 mg, 0.119 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.1 mg, 0.011 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 1:4) to provide cycloadduct **13** (54.6 mg, 0.107 mmol, 90%) as a white solid (mp 112–114 °C). R_f 0.13 (EtOAc/hexanes = 1:4); IR (CH_2Cl_2, NaCl) 3054 (w), 3027 (w), 2985 (w), 2954 (w), 1760 (vs), 1722 (vs), 1204 (vs), 1155 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.19–7.40 (m, 10H), 6.80 (AB_q, 2H, J = 9.0, 2.4 Hz), 3.76 (s, 3H), 3.27 (br s, 1H), 2.94–2.96 (m, 2H), 2.87 (br s, 1H), 2.38 (s, 3H), 2.28 (s, 3H), 2.13 (d, 1H, J = 9.8 Hz), 1.78 (d, 1H, J = 9.7 Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 169.1, 169.0, 154.1, 142.34, 142.29, 141.0, 140.7, 139.4, 132.9, 132.6, 129.6, 129.0, 127.9, 127.3, 127.05, 127.02, 126.8, 120.10, 120.06, 53.1, 47.2, 41.5, 40.8, 39.1, 20.9, 20.7. HRMS (CI) calcd for $C_{31}H_{27}NO_6$ ($(M+H)^+$): 510.1917; found: 510.1923. Anal. Calcd for $C_{31}H_{27}NO_6$ = C, 73.07%; H, 5.34%; found = C, 73.40%; H, 5.21%.

4.2.13. Cycloadduct 14. Following the above general procedure (D) with alkene **4e** (32.9 mg, 0.135 mmol), ynamide **3e** (22.7 mg, 0.0903 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.1 mg, 0.011 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (EtOAc/hexanes = 3:7) to provide cycloadduct **14** (20.4 mg, 0.0412 mmol, 46%) as a white solid (mp 152–153 °C). R_f 0.42 (EtOAc/hexanes = 3:7); IR (CH_2Cl_2, NaCl) 3060 (w), 2968 (w), 1729 (s), 1691 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.05–7.41 (m, 12H), 6.66–6.93 (m, 2H), 5.11 (m, 2H), 3.77 (s, 3H), 3.19 (br d, 1H, J = 3.5 Hz), 2.74 (br s, 1H), 1.36 (s, 3H), 1.25 (s, 6H). HRMS (CI) calcd for $C_{31}H_{30}N_2O_4$ ($(M+H)^+$): 495.2284; found: 495.2280. Anal. Calcd for $C_{31}H_{30}N_2O_4$ = C, 75.28%; H, 6.11%; found = C, 75.55%; H, 6.01%.

4.2.14. Cycloadduct 15. Following the above general procedure (D) with alkene **4f** (47.0 mg, 0.326 mmol), ynamide **3e** (26.5 mg, 0.105 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.6 mg, 0.012 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:19–1:4) to provide cycloadduct **15** (37.2 mg, 0.0872 mmol, 83%) as a white solid (mp 164–166 °C). R_f 0.22 (EtOAc/hexanes = 1:9); IR (CH_2Cl_2, NaCl) 3055 (m), 3026 (m), 2993 (m), 2952 (m), 1727 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.54 (d, 2H, J = 7.8 Hz), 7.06–7.46 (m, 12H), 5.30 (s, 1H), 5.17 (s, 1H), 3.91 (s, 3H), 3.39 (d, 1H, J = 3.6 Hz), 3.01 (d, 1H, J = 3.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.2, 145.3, 139.5, 133.4, 132.4, 128.8, 127.8, 127.5 (br), 127.1, 126.7, 126.63, 126.57, 126.5, 119.9, 119.6, 77.2, 76.1, 53.4, 45.9, 43.3. HRMS (CI) calcd for $C_{26}H_{21}NO_3$ ($(M+H)^+$): 396.1600; found: 396.1609. Anal. Calcd for $C_{26}H_{21}NO_3$ = C, 79.97%; H, 5.35%; found = C, 79.11%; H, 5.30%.

4.2.15. Cycloadduct 16. Following the above general procedure (D) with alkene **4g** (47.2 mg, 0.256 mmol), ynamide **3e** (27.1 mg, 0.108 mmol), THF (0.3 mL), and Cp*RuCl(COD) (4.9 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 60 °C for 72 h. The crude product was purified by column chromatography (gradient EtOAc/hexanes = 1:19–2:3) to provide cycloadduct **16** (47.0 mg, 0.102 mmol, 94%) as a white solid (mp 130–133 °C). R_f 0.30 (EtOAc/hexanes = 2:3); IR (CH_2Cl_2, NaCl) 3061 (w), 2981

(m), 2928 (m), 2892 (m), 2875 (m), 2811 (w), 1722 (vs), 1302 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, 2H, J= 7.8 Hz), 7.21–7.27 (m, 2H), 7.02–7.13 (m, 4H), 6.85–6.94 (m, 2H), 4.40 (s, 1H), 4.21 (s, 1H), 3.79 (s, 3H), 3.34–3.48 (m, 5H), 3.36 (s, 3H), 3.34 (s, 3H), 2.94 (d, 1H, J=3.7 Hz), 2.10–2.20 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.4, 139.7, 132.3, 131.7, 128.9, 128.7, 127.7, 126.9, 126.1, 125.9, 77.3, 75.7, 71.00, 70.97, 58.85, 58.75, 53.3, 50.8, 45.4, 44.8, 44.2. HRMS (CI) calcd for $C_{26}H_{29}NO_5$ ($(M+H)^+$): 436.2124; found: 436.2130. Anal. Calcd for $C_{26}H_{29}NO_5$=C, 71.70%; H, 6.71%; found=C, 71.44%; H, 6.98%.

4.2.16. Cycloadduct 21. Following the above general procedure (D) with norbornene **4a** (54.1 mg, 0.575 mmol), ynamide **22** (54.6 mg, 0.207 mmol), THF (0.60 mL), and Cp*RuCl(COD) (5.0 mg, 0.013 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=3:7) to give the cycloadducts **21** as an inseparable mixture of diastereoisomers (60.4 mg, 0.169 mmol, 83%, dr=72:28 measured by 400 MHz ^1H NMR) as pale yellow oil. R_f 0.37 (EtOAc/hexanes=3:7); IR (neat) 3065 (w), 3032 (w), 2949 (m), 2872 (w), 1762 (s), 1648 (w), 1395 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.18–7.36 (m, 8H), 7.08–7.17 (m, 0.56H), 6.93–6.97 (m, 1.44H), 5.11–5.15 (m, 1H), 4.74 (app t, 0.28H, J=8.8 Hz), 4.73 (app t, 0.72H, J= 8.8 Hz), 4.22 (dd, 0.72H, J=8.8, 5.8 Hz), 4.18 (dd, 0.28H, J=8.8, 5.8 Hz), 2.86 (br d, 0.72H, J=3.6 Hz), 2.57 (br d, 0.56H), 2.50 (br d, 0.72H, J=3.6 Hz), 2.18 (br s, 0.72H), 2.06 (br s, 0.72H), 2.02 (br s, 0.56H), 1.46–1.58 (m, 2H), 1.27 (d, 0.28H, J=10.4 Hz), 1.14–1.23 (m, 2H), 0.85 (d, 0.72H, J=10.4 Hz), 0.79 (d, 0.28H, J=10.4 Hz), 0.74 (d, 0.72H, J=10.4 Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 154.94, 154.91, 138.6, 134.9, 133.5, 130.3, 129.3, 128.8, 128.7, 128.6, 128.04, 127.97, 127.94, 127.89, 127.84, 127.76, 127.43, 127.35, 127.1, 126.9, 126.5, 126.2, 70.4, 70.2, 59.6, 58.7, 55.9, 48.6, 48.5, 46.3, 44.8, 35.4, 35.0, 34.1, 34.0, 30.3, 29.8, 28.10, 28.07, 28.03, 28.0. HRMS (m/z) for $C_{24}H_{23}NO_2$ calcd 357.1729, found 357.1720. Anal. Calcd for $C_{24}H_{23}NO_2$=C, 80.64%; H, 6.49%; found C, 80.78%; H, 6.30%.

The 1:1 diastereomeric mixture of **21** was prepared as follow: to a flask under nitrogen containing K_3PO_4 (52.4 mg, 0.247 mmol), CuI (3.3 mg, 0.017 mmol) and (*R*)-(−)-4-phenyl-2-oxazolidinone (23.4 mg, 0.129 mmol) was added a solution of **20**[17g] (32.5 mg, 0.101 mmol) in toluene (0.4 mL) via cannula. *N*,*N*′-dimethylethylenediamine (15 μL, 0.14 mmol), prior to heat the reaction mixture at 90 °C for 20 h. The crude mixture was then cooled to room temperature and purified by column chromatography to give **21** as an inseparable mixture of diastereoisomers (25.1 mg, 0.0702 mmol, 70%, dr=53:47 measured by 400 MHz ^1H NMR).

4.2.17. Cycloadduct 26. Following the above general procedure (D) with norbornene **4a** (29.7 mg, 0.315 mmol), ynamide **7** (28.1 mg, 0.0848 mmol), THF (0.40 mL), and Cp*RuCl(COD) (3.4 mg, 0.0089 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=1:4) to give the cycloadducts **26** as an inseparable mixture of diastereoisomers (26.1 mg, 0.0611 mmol, 72%, dr=58:42 measured by 400 MHz ^1H NMR) as pale yellow oil. R_f 0.49 (EtOAc/hexanes=1:4); IR (neat) 3055 (w), 3026 (w), 2952 (s), 2868 (m), 1760 (vs), 1650 (m), 1404 (vs) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.29–7.34 (m, 2H), 7.21–7.24 (m, 3H), 4.43 (d, 0.42H, J= 8.6 Hz), 4.41 (d, 0.58H, J=8.6 Hz), 4.33 (dd, 0.42H, J= 8.4, 3.6 Hz), 4.28 (dd, 0.58H, J=8.6, 4.4 Hz), 4.17–4.21 (m, 1H), 3.50 (dd, 0.42H, J=10.4, 5.2 Hz), 3.46 (dd, 0.58H, J=10.6, 4.7 Hz), 3.40 (dd, 0.58H, J=10.4, 3.0 Hz), 3.29 (dd, 0.42H, J=10.6, 2.4 Hz), 3.02 (br d, 0.58H, J=3.5 Hz), 2.79 (br d, 0.42H, J=3.5 Hz), 2.72 (br d, 0.42H, J= 3.4 Hz), 2.59 (d, 0.58H, J=3.6 Hz), 2.48 (br s, 0.42H), 2.41 (br s, 0.58H), 2.19 (br s, 0.58H), 2.02 (br s, 0.42H), 1.53–1.64 (m, 3H), 1.12–1.18 (m, 2H), 1.06 (d, 0.58H, J= 10.3 Hz), 1.02 (d, 0.42H, J=10.2 Hz), 0.83 (s, 3.78H), 0.81 (s, 5.22H), −0.06 (s, 1.26H), −0.08 (s, 1.74H), −0.09 (s, 1.26H), −0.10 (s, 1.74H); ^{13}C NMR (APT, $CDCl_3$, 100 MHz) major diastereomer: δ 155.0, 134.8, 128.1, 128.0, 127.2, 126.99, 126.3, 65.1, 55.5, 48.8, 46.4, 45.2, 36.3, 34.3, 30.6, 28.26, 28.1, 25.6, −5.6; minor diastereomer: δ 155.1, 133.8, 128.7, 128.2, 127.5, 127.1, 125.2, 65.1, 60.9, 55.9, 48.5, 45.2, 35.5, 34.5, 30.5, 28.35, 27.8, 25.6, −5.8. HRMS (m/z) for $C_{25}H_{35}NO_3Si$ calcd 425.2386, found 425.2367. Anal. Calcd for $C_{25}H_{35}NO_3Si$=C, 70.55%; H, 8.29%; found C, 70.40%; H, 8.44%.

4.2.18. Cycloadduct 27. Following the above general procedure (D) with norbornene **4a** (62.6 mg, 0.665 mmol), ynamide **8** (46.8 mg, 0.215 mmol), THF (0.50 mL), and Cp*RuCl(COD) (7.3 mg, 0.019 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=3:2) to give the cycloadducts **27** as an inseparable mixture of diastereoisomers (54.6 mg, 0.174 mmol, 81%, dr=71:29 measured by 400 MHz ^1H NMR) as a pale yellow oil. R_f 0.47 (EtOAc/hexanes=3:2); IR (neat) 3058 (w), 2953 (m), 2870 (m), 1739 (s), 1649 (m), 1409 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.24–7.31 (m, 5H), 4.43–4.47 (m, 2H), 4.20–4.23 (m, 1H), 3.50–3.63 (m, 1H), 3.38–3.48 (m, 1H), 2.99 (br s, 0.71H), 2.77 (br s, 0.29H), 2.73 (br s, 0.29H), 2.62 (br s, 0.71H), 2.40 (br s, 1H), 2.16 (br s, 0.71H), 2.08 (br s, 0.29H), 1.99 (br s, 0.29H), 1.89 (br s, 0.71H), 1.52–1.69 (m, 3H), 1.02–1.25 (m, 3H); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) major diastereomer: δ 155.1, 134.3, 128.5, 128.2, 127.42, 127.38, 127.1, 64.9, 60.9, 55.6, 48.8, 46.0, 36.0, 34.1, 30.4, 28.2, 28.1; minor diastereomer: δ 155.2, 133.4, 128.3, 128.06, 128.01, 127.34, 127.24, 65.1, 60.8, 56.1, 48.8, 45.1, 35.3, 34.4, 30.5, 28.3, 27.9. HRMS (m/z) for $C_{19}H_{21}NO_3$ calcd 311.1521, found 311.1530. Anal. Calcd for $C_{19}H_{21}NO_3$=C, 73.29%; H, 6.80%; found C, 73.44%; H, 6.71%.

4.2.19. Cycloadduct 28. Following the above general procedure (D) with norbornene **4a** (74.3 mg, 0.789 mmol), ynamide **23** (65.2 mg, 0.237 mmol), THF (0.40 mL), and Cp*RuCl(COD) (5.4 mg, 0.014 mmol). The reaction mixture was stirred in the dark at 65 °C for 68 h. The crude product was purified by column chromatography (EtOAc/hexanes=3:7) to give an inseparable mixture cycloadducts **28** as an inseparable mixture of diastereoisomers (72.0 mg, 0.195 mmol, 82%, dr=74:26 measured by 400 MHz ^1H NMR) as a pale yellow oil. R_f 0.51 (EtOAc/hexanes=3:7); IR (neat) 3065 (m), 2953 (s), 2871 (m), 1751 (s), 1651 (s),

1385 (s), 1266 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) 7.38–7.39 (m, 1H), 7.24–7.33 (m, 5H), 7.18–7.22 (m, 1H), 7.10–7.14 (m, 1H), 7.04–7.06 (m, 1H), 5.58 (d, 0.26H, J= 6.5 Hz), 5.57 (d, 0.74H, J=7.3 Hz), 5.35–5.41 (m, 1H), 3.33–3.41 (m, 2H), 3.12 (br d, 0.74H, J=3.6 Hz), 2.86 (br d, 0.26H, J=3.6 Hz), 2.73 (br d, 0.26H, J=3.5 Hz), 2.68 (br d, 0.74H, J=3.6 Hz), 2.60 (br s, 0.26H), 2.48 (br d, 0.74H, J=3.1 Hz), 2.13 (br d, 0.74H, J=2.9 Hz), 2.11 (br s, 0.26H), 1.57–1.70 (m, 3H), 1.14–1.23 (m, 2H), 1.08 (d, 0.26H, J=10.3 Hz), 1.00 (d, 0.74H, J=10.4 Hz); ^{13}C NMR (APT, $CDCl_3$, 75 MHz) δ 154.1, 154.0, 140.04, 139.93, 139.0, 138.6, 134.6, 133.5, 129.5, 129.4, 128.5, 128.2, 127.9, 127.7, 127.63, 127.55, 127.4, 127.3, 127.2, 127.1, 127.0, 126.6, 125.6, 125.33, 125.26, 78.1, 77.8, 63.3, 63.2, 49.1, 49.0, 46.2, 44.9, 38.6, 38.1, 36.2, 35.6, 34.3, 34.1, 30.6, 30.3, 28.3, 28.2, 28.0, 27.8. HRMS (m/z) for $C_{25}H_{23}NO_2$ calcd 369.1729, found 369.1717. Anal. Calcd for $C_{25}H_{23}NO_2$=C, 81.27%; H, 6.27%; found C, 81.36%; H, 6.14%.

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