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Intramolecular Morita–Baylis–Hillman adducts via sequential MBH and ring-closing-metathesis reactions

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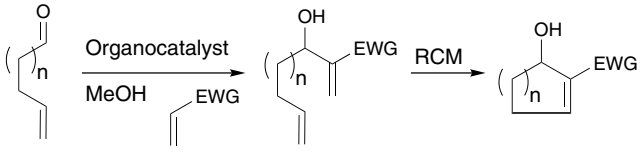
Abstract—Using a tandem Morita–Baylis–Hillman (MBH) and ring-closing-metathesis (RCM) sequence, an alternative high yielding method for the construction of intramolecular Morita–Baylis–Hillman (IMBH) mono- and bicyclic functionalized cycloalkenols is reported.

Synthetic design in organic chemistry strives for the maximization of complexity with a minimization of operations. Reactions that occur in tandem or generate functionality that is easily transformed in sequential processes provide an opportunity to rapidly increase complexity in organic structures. Use of the Morita–Baylis–Hillman[1] (MBH) reaction in sequence with other processes such as the Heck reaction, Claisen rearrangements, cycloadditions, metathesis, and free radical reactions have greatly enhanced its value.[2–6] Morita–Baylis–Hillman adducts serve as important precursors for the synthesis of diverse multifunctional molecules. For instance, the MBH acetate, prepared from the corresponding allylic alcohol, has been found to be an outstanding intermediate for allylic functionalization. In particular, these reactions include organo-catalytic allylic alkylation,[7] allylic amination,[8] Pd catalyzed cross coupling,[9] nucleophilic displacement,[10] and cationic cyclizations.[11]

Ring-closing metathesis (RCM) of allylated MBH adducts has provided an additional means for synthesizing heterocyclic rings such as pyrrolines,[12] dihydrofurans,[13] and dihydropyrroles.[13,14] While the intermolecular MBH has been studied in depth,[2] the intramolecular version has not been the subject of a detailed evaluation. Both Lewis acid mediated and organocatalyzed intramolecular Morita–Baylis–Hillman (IMBH) reactions have been reported.[15,16] However, these routes to IMBH adducts are highly substrate dependent and somewhat limited.[17] An alternative route involves the MBH reaction of an alkenyl aldehyde, which then sets the stage for subsequent ring-closing metathesis[18] generating a product that mimics an IMBH reaction (Eq. 1).



(1)

Herein, we now describe a sequential MBH/RCM reaction sequence that gives mono- and bicyclic functionalized cycloalkenols with high efficiency. Optimal conditions for the MBH reaction (Eq. 1) were found after surveying a series of well-established organocatalysts in different solvents. Use of amine-based catalysts such as DABCO, in aqueous or organic media, as well as tributylphosphine and phenol in THF yielded inferior results when compared to the conditions reported by Aggarwal et al.[19] (quinuclidine, MeOH, rt). Treatment of 4-pentenal **1** with 0.25 equiv of quinuclidine and 0.75 equiv of MeOH, and stirring for 6 h at ambient temperature in the presence of 1.2 equiv of the methyl acrylate gave diene **15** in excellent yield. Subsequent RCM with 10 mol % of Grubbs 2nd generation catalyst[18] in DCM at reflux afforded the five-membered ring adduct in moderate yield (Table 1, entry 1). By comparison, the MBH reaction was lower yielding when methyl

Keywords: Morita–Baylis–Hillman reaction; Cycloalkenols; Cyclization; Allylic alcohols; Ring-closing metathesis.
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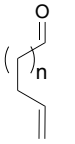
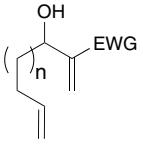
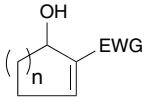
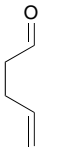
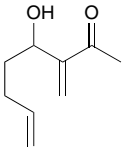
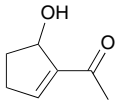
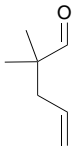
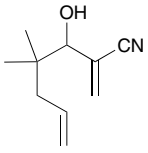
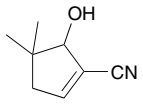
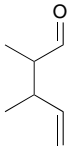
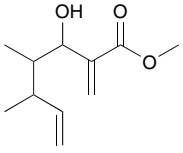
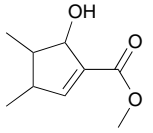
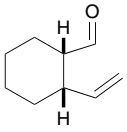
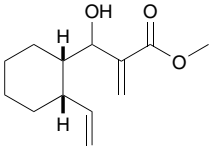
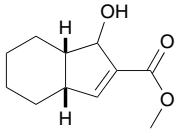
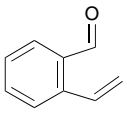
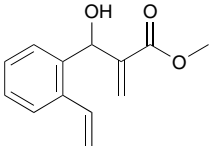
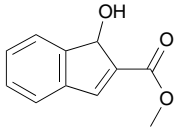
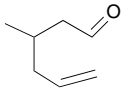
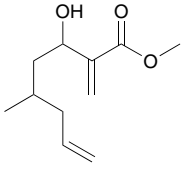
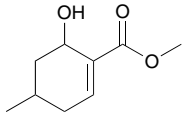
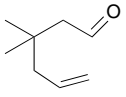
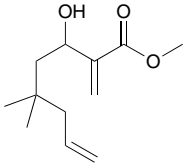
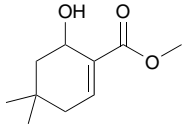
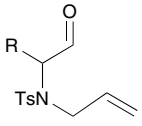
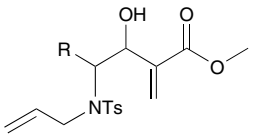
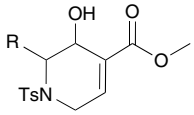
Table 1. Morita–Baylis–Hillman/ring-closing metathesis reactions

Entry	Aldehyde		Baylis Hillman Adduct[a]		Yield (%)	RCM product[b]		Yield (%)
								
1	$n=1$	**1**	EWG = CO_2Me $n=1$	**15**	95	$n=1$	**30**	46
2	$n=2$	**2**	EWG = CO_2Me $n=2$	**16**	84	$n=2$	**31**	67
3	$n=3$	**3**	EWG = CO_2Me $n=3$	**17**	89	$n=3$	**32**	66
4	$n=1$	**4**	EWG = CN $n=1$	**18**	65	$n=1$	**33**	50
5	$n=2$	**5**	EWG = CN $n=2$	**19**	72	$n=2$	**34**	87
6	$n=3$	**6**	EWG = CN $n=3$	**20**	83	$n=3$	**35**	81
7		**1**		**21**	54		**36**	88
8		**7**		**22**	34		**37**	91
9		**8**		**23**	60[c]		**38**	45[c]
10		**9**		**24**	22		**39**	66
11		**10**		**25**	83		**40**	92
12		**11**		**26**	82[c]		**41**	87[c]
13		**12**		**27**	84		**42**	87
								
14	R = H	**13**	R = H	**28**	78	R = H	**43**	87
15	R = Me	**14**	R = Me	**29**	80[d]	R = Me	**44**	87[d]

[a] Reaction conditions: 0.25 equiv quinuclidine, 0.75 equiv MeOH, 1.2 equiv activated alkene, rt, 6–12 h-until complete by TLC analysis.
[b] Reaction conditions: 10 mol % Grubbs II, 0.01 M DCM, reflux. Hoveyda–Grubbs catalyst[18] was used for the metathesis of dienes **18**–**22**.
[c] Mixture of isomers.
[d] 8:1 mixture of isomers.

vinyl ketone was used in place of methyl acrylate as the activated alkene (Table 1, entry 7 vs entry 1). However, the corresponding RCM result was significantly better in the latter case.

With this result in hand, six- and seven-membered ring precursors **16** and **17** were synthesized via MBH reactions in excellent yields. These two dienes **16** and **17**, which lacked substitution on the tether, cyclized efficiently to give the cyclic alkenols **31** and **32** respectively, in good yields.[20] Unfortunately, attempts to generate the analogous eight- and nine-membered rings led solely to dimerization of the diene.

Probing the scope of the method, we discovered that substitution on the tether had little consequence in the MBH reaction and subsequently exhibited an overall positive effect on the cyclization step. Reactions to form five-membered substituted carbocycles, i.e., **37**, **38**, **39** and **40**, produced moderate to excellent yield of the desired RCM product. Reactions which generated the six-membered carbocycles **41** and **42** were also high yielding. In the cases examined, RCM to form cyclohexenols proceeded with greater efficiency than those forming cyclopentenols.[21] Furthermore, the syntheses of heterocyclic sulfonamides **43** and **44** were achieved in high yield from dienes **28** and **29**.

After success with both methyl acrylate and methyl vinyl ketone as substrates, it was found that when using acrylonitrile as an alternative activated alkene, yields were yet again very good for the MBH step. In addition, a significant increase in yield was achieved in the RCM of enones **19** and **20** generating carbocycles **34** and **35** when compared to the RCM of **16** and **17** giving cycloalkenols **31** and **32**, respectively. Overall excellent yields of the allylic alcohols (**30**–**44**) were formed in most cases (Table 1).

In summary, we have described a new approach to functionalized hetero- and carbocyclic alkenols. Combining the MBH and RCM reactions in tandem creates IMBH adducts in good to excellent overall yield, thus providing a successful alternative route to the highly substrate dependant IMBH reaction.

Acknowledgments

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21. ^{1}H NMR spectral data ($CDCl_3$) [**16**, **19**, **30**, **33**—Ref. 20; **23**, **26**, **38**—inseparable mixtures of isomers; **31**, **34**—Villieras, J.; Rambaud, M.; Graff, M. *Synth. Commun.* **1986**, *16*, 149; **15**, **18**, **33**, **36**—Graff, M.; Dilaimi, A.; Seguineau, P.; Rambaud, M.; Villieras, J. *Tetrahedron Lett*. **1986**, *27*, 1577].
Compound **16**: 500 MHz ^{1}H NMR: δ 1.44 (m, 1H, CH_2CHHCH_2), 1.58 (m, 1H, CH_2CHHCH_2), 1.68 (m, 2H, CH_2CH_2CHOH), 2.10 (dt, 2H, $J = 6.8$, 6.8, $CH_2CH_2CH{=}C$), 3.80 (s, 3H, OCH_3), 4.40 (broad t, 1H, $J = 6$ $CH_2CHOHC{=}C$), 4.97 (dm, 1H, $J = 10.3$, $CH{=}CHH$), 5.02 (dd, 1H, $J = 17.1$, 1.5, $CH{=}CHH$), 5.81 (ddt, 1H, $J = 17.1$, 10.3, 6.8, $CH_2CH{=}CH_2$), 5.82 (partly obscured s, 1H, $C{=}CHH$), 6.25 (s, 1H, $C{=}CHH$).
Compound **17**: 500 MHz ^{1}H NMR: δ 1.35–1.49 (m, 4H, $CHOHCH_2CH_2CH_2$, $CH_2CH_2CH_2CH{=}C$), 1.64–1.69 (m, 2H, CH_2CH_2CHOH), 2.07 (dt, 2H, $J = 6.8$, 6.8, $CH_2CH_2CH{=}C$), 3.80 (s, 3H, OCH_3), 4.39 (dt, 1H, $J = 6.4$, 6.8, $CH_2CHOHC{=}C$), 4.95 (dm, 1H, $J = 10.3$, $CH{=}CHH$), 5.01 (ddt, 1H, $J = 17.0$, 1.4, 1.4, $CH{=}CHH$), 5.81 (ddt, 1H, $J = 17.1$, 10.3, 6.8, $CH_2CH{=}CH_2$), 5.82 (partly obscured s, 1H, $C{=}CHH$), 6.25 (s, 1H, $C{=}CHH$).
Compound **19**: 500 MHz ^{1}H NMR: δ 1.78 (m, 3H, $CH_2CH_2CH_2$, OH), 1.87 (m, 2H, CH_2CH_2CHOH), 2.10 (m, 2H, $CH_2CH_2CH{=}C$), 4.40 (dd, 1H, $J = 8.1$, 5.4, $CH_2CHOHC{=}C$), 5.05 (d, 1H, $J = 10.3$, $CH{=}CHH$), 5.10

(dd, 1H, $J = 17.6, 1.5$, CH=CH*H*), 5.84 (ddt, 1H, $J = 16.9, 10.3, 6.6$, CH_2CH=CH_2), 6.00 (s, 1H, C=C*H*H), 6.02 (d, $J = 1.5$, 1H, C=CH*H*).

Compound **20**: 500 MHz ^{1}H NMR: δ 1.41–1.50 (m, 2H, $CH_2CH_2CH_2CH$=C), 1.64–1.80 (m, 4H, CHO-$HCH_2CH_2CH_2$, CH_2CH_2CHOH), 2.07 (dt, 2H, $J = 7.3, 7.3$, CH_2CH_2CH=C), 4.39 (dd, 1H, $J = 7.3, 5.1$, CH_2CHOHC=C), 4.95 (partially obscured dt, 1H, $J = 10.3, 2.2$, CH=C*H*H), 5.01 (dq, 1H, $J = 16.9, 1.5$, CH=CH*H*), 5.8 (ddt, 1H, $J = 16.6, 6.6, 7.6$, CH_2CH=CH_2), 5.98 (s, 1H, C=C*H*H), 6.0 (d, 1H, $J = 1.5$, C=CH*H*).

Compound **21**: 500 MHz ^{1}H NMR: δ 1.65–1.72 (m, 2H, $CHCH_2CH_2$), 2.16 (m, 2H, CH_2CH_2CH=C), 2.36 (s, 3H, CCH_3), 4.45 (t, 1H, $J = 7$, 6, CH_2CHC=C), 4.97 (d, 1H, $J = 10$, CH=C*H*H), 5.04 (d, 1H, $J = 17$, CH=CH*H*), 5.82 (ddt, 1H, $J = 17.1, 9.3, 6.4$, CH_2CH=CH_2), 6.02 (s, 1H, C=C*H*H), 6.11 (s, 1H, C=CH*H*).

Compound **22**: 500 MHz ^{1}H NMR: δ 0.99 (s, 3H, CCH_3), 1.00 (s, 3H, CCH_3), 2.06 (dd, 1H, $J = 13.7$, 7.3, CCH_2CH=C), 2.24 (dd, 1H, $J = 13.7, 7.8$, CCH_2CH=C), 4.06 (s, 1H, CC*H*C=C), 5.12 (d, 1H, $J = 17.7$, CH=C*H*H), 5.13 (d, 1H, $J = 10.8$, CH=CH*H*), 5.87 (ddt, 1H, $J = 16.1, 10.7, 7.3$, CH_2CH=CH_2), 5.99 (s, 1H, C=C*H*H), 6.14 (s, 1H, C=CH*H*).

Compound **24**: 500 MHz ^{1}H NMR: δ 1.13–1.75 (m, 9H, $CH_2CH_2CH_2$, $CH_2CH_2CH_2$, $CH_2CH_2CH_2$, $CH_2CH_2CH_2$, $CH_2CHCHCH$), 2.14 (m, 1H, $CH_2CHCHCH$=), 3.78 (s, 3H, OCH_3), 4.81 (d, 1H, $J = 1$, $CHCHC$=), 5.06 (dd, 1H, $J = 10.3$, 2.0, CH=C*H*H), 5.14 (dd, 1H, $J = 17.1$, 1.5, CH=CH*H*), 5.76 (ddd, 1H, $J = 16.6$, 9.5, 9.8, $CHCH$=CH), 5.88 (dd, 1H, $J = 1.5$, 1.5, C=C*H*H), 6.35 (s, 1H, $J = 1.5$, 1.5, C=CH*H*).

Compound **25**: 500 MHz ^{1}H NMR: δ 3.79 (s, 3H, OCH_3), 5.33 (dd, 1H, $J = 10.8$, 1.5, CH=C*H*H), 5.60 (t, 1H, $J = 1$, ArCHC), 5.66 (dd, $J = 17.3$, 1.5, CH=CH*H*), 5.92 (s, 1H, C=C*H*H), 6.37 (s, 1H, C=CH*H*), 6.94 (dd, 1H, $J = 17.3$, 11.2, $ArCH$=CH_2), 7.33 (dd, 2H, $J = 4.6$, 4.9, aromatics), 7.47 (dd, 1H, $J = 4.6$, 4.4, aromatics), 7.52 (dd, 1H, $J = 4.7$, 4.9, aromatics).

Compound **27**: 500 MHz ^{1}H NMR: δ 0.98 (s, 3H, CCH_3), 1.00 (s, 3H, CCH_3), 1.51 (dd, 1H, $J = 14.8$, 2.8, CC*H*H-CHOH), 1.57 (dd, 1H, $J = 14.6$, 8.7, CCH*H*CHOH), 2.05 (dd, 1H, $J = 13.1$, 6.3, CC*H*HCH=CH_2), 2.10 (dd, 1H, $J = 13.1$, 6.3, CCH*H*CH=CH_2), 3.78 (s, 3H, OCH_3), 4.59 (dd, 1H, $J = 8.4$, 2.8, CH_2CHC=C), 5.02 (dm, 1H, $J = 16.7$, CH=C*H*H), 5.03 (dm, 1H, $J = 10.1$, CH=CH*H*), 5.80 (obscured s, 1H, C=C*H*H), 5.84 (ddt, 1H, $J = 16.7, 10.4, 7.3$, CH_2CH=CH_2), 6.18 (s, 1H, C=CH*H*).

Compound **28**: 500 MHz ^{1}H NMR: δ 2.45 (s, 3H, $ArCH_3$), 3.25 (dd, 1H, $J = 14.5, 7.8$, TsNC*H*HCHOHC=C), 3.35 (dd, 1H, $J = 14.5, 3.4$, TsNCH*H*CHOHC=C), 3.75 (s, 3H, OCH_3), 3.91 (dd, 2H, $J = 4.0, 6.0$, $TsNCH_2CH$=C), 4.69 (dd, 1H, $J = 7.6, 3.9$, CH_2CHOHC=C), 5.18 (dm, 1H, $J = 10$, CH=C*H*H), 5.21 (dm, 1H, $J = 15.4$, CH=CH*H*), 5.68 (ddt, 1H, $J = 17.1, 9.8, 6.3$, CH_2CH=CH_2), 6.11 (t, 1H, $J = 1.8$, C=C*H*H), 6.39 (t, 1H, $J = 1.2$, C=CH*H*), 7.32 (d, 2H, $J = 13$, aromatics), 7.73 (d, 2H, $J = 13.5$, aromatics).

Compound **29**: 500 MHz ^{1}H NMR: δ 1.08 (d, 3H, $J = 6.8$, CH_3CH), 2.44, (s, 3H, $ArCH_3$), 3.70 (dd, 1H, $J = 16.2, 8.4$, TsNC*H*HCH=CH_2), 3.83 (s, 3H, OCH_3), 3.97 (ddt, 1H, $J = 16.2, 5.4, 1.8$, TsNCH*H*CH=CH_2), 4.09 (qd, 1H, $J = 6.8$, 6.8, $TsNCHCH_3CH$), 4.50 (d, 1H, $J = 5.9$, CHC*H*OHC), 5.14 (dm, 1H, $J = 10.3$, CH=C*H*H), 5.21 (dm, 1H, $J = 17.1$, CH=CH*H*), 5.81 (ddt, 1H, $J = 17.1, 10.3, 7.8$, CH_2CH=CH_2), 5.93 (dm, 1H, C=C*H*H), 6.38 (dm, 1H, C=CH*H*), 7.29 (d, 2H, $J = 7.8$, aromatics), 7.71 (d, 2H, $J = 7.8$, aromatics).

Compound **31**: 500 MHz ^{1}H NMR: δ 1.60–1.65 (m, 1H, CH_2CHHCH_2), 1.75–1.86 (m, 3H, CH_2CHHCH_2, $CHCH_2CH_2$), 2.14–2.19 (m, 1H, CH_2CHHCH=C), 2.28 (ddt, 1H, $J = 20$, 4.9, 4.9, CH_2CHHCH=C), 3.79 (s, 3H, OCH_3), 4.56 (broad t, 1H, $J = 5$, CH_2CHOHC=C), 7.13 (t, 1H, $J = 4$, CH_2CH=C).

Compound **32**: 500 MHz ^{1}H NMR: δ 1.54–1.64 (m, 2H, $CHOHCH_2CH_2CH_2$), 1.70–1.88 (m, 4H, CH_2CH_2-CH_2CH=C, $CHOHCH_2CH_2$), 2.03–2.16 (m, 1H, CH_2CH-HCH=C), 2.26 (ddt, 1H, $J = 20.4$, 4.2, 4.2, CH_2CHHCH=C), 3.75 (s, 3H, OCH_3), 4.53 (m, 1H, CH_2CHOHC), 7.09 (t, 1H, $J = 3.6$, CH_2CH=C).

Compound **35**: 500 MHz ^{1}H NMR: δ 1.43–1.51 (m, 1H, m, 1H, CH_2CHHCH_2CH=C), 1.63–1.71 (m, 2H, CHO-$HCH_2CH_2CH_2$), 1.74–1.82 (m, 1H, $CHOHCHHCH_2$), 1.89–1.94 (m, 1H, $CHOHCHHCH_2$), 1.96–2.03 (m, 1H, CH_2CHHCH_2CH=C), 2.22 (m, 1H, CH_2CHHCH=C), 2.42 (ddt, 1H, $J = 16.1, 9.5, 2.2$, CH_2CHHCH=C), 4.48 (d, 1H, $J = 9.5$, CH_2CHOHC), 6.81 (dt, 1H, $J = 6.8$, 1.7 CH_2CH=C).

Compound **37**: 500 MHz ^{1}H NMR: δ 1.08 (s, 3H, CH_3C), 1.11 (s, 3H, CH_3C), 2.28 (ddd, 2H, $J = 18.6, 3.0, 1.2$, CC*H*HCH=C), 2.44 (dd, $J = 18.6$, 2.4, 2.4, CCH*H*CH=C), 4.38 (broad s, 1H, CC*H*OHC=), 6.77 (t, 1H, $J = 4$, CH_2CH=C).

Compound **39**: 500 MHz ^{1}H NMR: δ 1.25–1.36 (m, 4H, $CHOHCHCH_2CH_2$, $CHOHCHCH_2CH_2CH_2$), 1.59–1.60 (m, 1H, $CHOHCHCH_2CH_2$), 1.81–1.84 (m, 2H, CH_2CH_2-CH_2CHCH=C), 1.99–2.04 (m, 2H, CH_2CH_2CHCH=C), 2.11–2.13 (m, 1H, CH_2CHCH=C), 3.78 (s, 3H, OCH_3), 4.60 (d, 1H, $J = 8.5$, $CHCHC$=C), 6.85 (broad s, 1H, CHC*H*=C).

Compound **40**: 500 MHz ^{1}H NMR: δ 3.90 (s, 3H, O=$COCH_3$), 5.45 (s, 1H, ArC*H*OHC), 7.53–7.46 (m, 3H, aromatics), 7.59 (s, 1H, ArC*H*=C), 7.63 (d, 1H, $J = 6.3$, aromatics).

Compound **41**: 500 MHz ^{1}H NMR: δ 1.00 (d, 3H, $J = 6.6$, $CHCH_3$), 1.35 (ddd, 1H, $J = 14.6$, 4.2, 12.6, CHC*H*HCHOH), 1.74 (dddd, 1H, $J = 19$, 10.2, 2.4, 1.2, CHC*H*HCH=C), 1.91–2.03 (m, 2H, $CH_2CHCH_3CH_2$, CHCH*H*CHOH), 2.36 (dddd, 1H, $J = 19.2$, 6.0, 5.4, 1.2, CHCH*H*CH=C), 3.77 (s, 3H, OCH_3), 4.56 (broad m, 1H, CH_2CHOHC=C), 7.09 (dd, 1H, $J = 5.4$, 2.4, CH_2CH=C).

Compound **42**: 500 MHz ^{1}H NMR: δ 0.91 (s, 3H, CH_3C), 1.04 (s, 3H, CH_3C), 1.51 (dd, 1H, $J = 13.2$, 8.4, CC*H*HCHOH), 1.83 (ddd, 1H, $J = 13.2$, 6.3, 2.1, CC*H*HCHOH), 2.0 (dddd, 1H, $J = 19.2$, 4.9, 1.7, 1.7, CC*H*HCH=C), 2.11 (ddd, 1H, $J = 19.5$, 3.0, 3.1, CCH*H*CH=C), 3.78 (s. 3H, OCH_3), 4.57 (m, 1H, CH_2CHOHC=C), 7.00 (ddd, 1H, $J = 4.9$, 3.8, 1.1, CH_2CH=C).

Compound **43**: 500 MHz ^{1}H NMR: δ 2.45 (s, 3H, $ArCH_3$), 3.15 (dd, 1H, $J = 12$, 4.4, TsNC*H*HCHOH), 3.41 (dd, 1H, $J = 12.2, 4.9$, TsNCH*H*CHOH), 3.62 (broad d, 1H, $J = 19$, $TsNCHHCH$=C), 3.79 (s, 3H, OCH_3), 3.91 (d, 1H, $J = 3.4$, TsNCH*H*CH=C), 4.63 (broad s, 1H, CH_2CHOHC=C), 6.94 (t, 1H, $J = 3.5$, CH_2CH=C), 7.35 (d, 2H, $J = 8$, aromatics), 7.71 (d, 2H, $J = 7$, aromatics).

Compound **44**: 500 MHz ^{1}H NMR: δ 0.87 (d, 3H, $J = 4.5$, CH_3CH), 2.43 (s, 3H, $ArCH_3$), 3.69 (dd, 1H, $J = 20$, 1.5, TsNC*H*HCH=C, $TsNCHCH_3CHOHC$=C), 3.80 (s, 3H, OCH_3), 4.28–4.37 (m, 3H, CHC*H*OHC=C, $TsNCHCH_3CHOHC$=C, TsNCH*H*CH=C), 7.02 (m, 1H, CH_2CH=C), 7.32 (d, 2H, $J = 8$, aromatics), 7.78 (d, 2H, $J = 7.5$, aromatics).