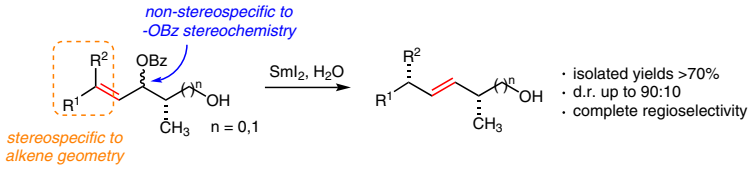
Synlett T. F. Stockdale, G. W. O'Neil Letter

Regio- and Diastereoselective Samarium-Mediated Allylic Benzoate Reductions

Trevor F. Stockdale
Gregory W. O'Neil*

Department of Chemistry, Western Washington University, Bellingham, WA, USA
oneilg@wwu.edu



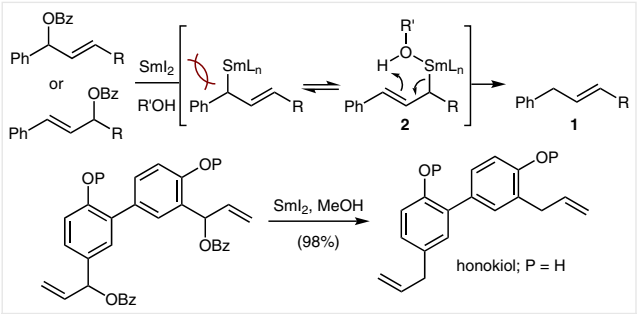
Received: 01.06.2017
Accepted after revision: 19.06.2017
Published online: 20.07.2017
DOI: 10.1055/s-0036-1590831; Art ID: st-2017-r0421-l

Abstract A regio- and diastereoselective samarium(II)-mediated reduction of allylic benzoates is described. Yields for the reactions are generally high with diastereoselectivities up to 90:10 and in some cases only a single regioisomer was obtained. The stereoselectivity of the reaction is proposed to arise from chelation of a hydroxyl-stereocenter and starting alkene geometry, with protonation occurring intramolecularly by samarium-bound water.

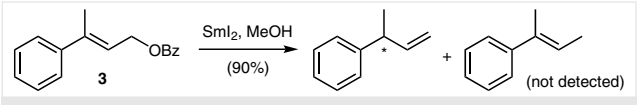
Key words samarium, reduction, stereoselective synthesis, regioselectivity, diastereoselectivity

Samarium diiodide (SmI_2) has emerged as one of the more useful and versatile reductants available to synthetic chemists,[1] capable of controllable (e.g. through the use of additives like HMPA or H_2O)[2] and selective reductions of a wide variety of functional groups.[3] Our group recently reported a SmI_2-mediated reductive removal of allylic benzoates leading selectively to non-conjugated olefin products of type **1** (Scheme 1).[4] The reaction is proposed to proceed via an organosamarium intermediate **2**, with regioselectivity controlled by sterics and intramolecular proton delivery from a samarium-coordinated proton donor (e.g. water or MeOH).[5] This method then featured as part of our synthesis of the biologically-relevant natural product honokiol, used to simultaneously install both allyl substituents found in the target compound.[6]

As an extension of that work, we began investigating the reaction applied to trisubstituted alkene substrates. For instance, treatment of allyl benzoate **3**[7] with SmI_2/MeOH led to its rapid and clean conversion to 3-phenyl-1-butene with complete regioselectivity by ^1H NMR analysis (Scheme 2). We recognized that this reaction generated a new stereocenter, and were intrigued about the possibility of adapting this general strategy into a stereoselective process. Herein we report the development of a regio- and diastereoselective samarium-mediated allylic benzoate reduction[8] using both Roche ester and lactate derived substrates. The reaction appears to be quite general, affording both aryl and alkyl products containing methyl or ethyl stereocenters in comparable yield and selectivities. Importantly, diastereoselectivities were independent of the initial benzoylated hydroxyl stereochemistry yet stereospecific with regard to the trisubstituted alkene geometry.



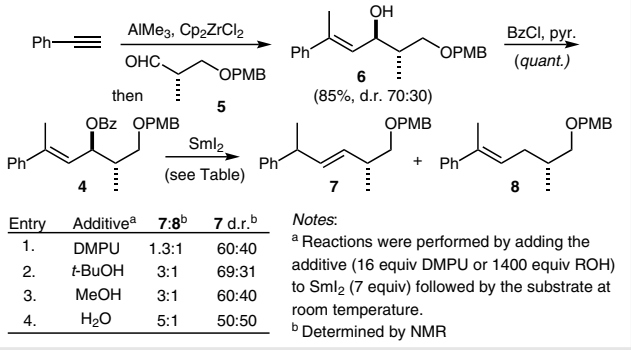
Scheme 1 Regioselective SmI_2 allyl benzoate reductions



Scheme 2 Reduction of a trisubstituted alkene allylic benzoate and formation of a new stereocenter (*)

Our initial investigations began with the PMB-protected *trans*-phenyl compound **4**, prepared by zirconium-catalyzed carboalumination of phenylacetylene[9] and trapping of the resulting vinylalane with aldehyde (*S*)-**5**[10] (Scheme 3). The stereochemistry of the newly formed hydroxyl in **6** for the major isomer is assumed to be *S* arising from chela-

tion control,[11] but was not rigorously determined as this stereocenter proved unimportant for the subsequent eliminations (*vide infra*). Benzoylation and treatment with SmI_2/ROH or SmI_2/DMPU (followed by quenching with H_2O) at room temperature led to rapid elimination, affording a mixture of alkene regioisomers generally in favor of the non-conjugated product **7** (up to 5:1). Careful analysis of the ^1H NMR spectra, however, revealed no appreciable levels of diastereoselectivity for any of the reactions.[12] The highest diastereomeric ratio (d.r.) was obtained when using *tert*-butanol (*t*-BuOH), however, this reaction proceeded with only modest regioselectivity and produced what we have tentatively characterized as dimerization products presumably due to a slower protonation event (similar products were also observed for the anhydrous DMPU entry).[13] The SmI_2/H_2O reaction was much cleaner in this regard (i.e. 5:1 regioselectivity and no dimerization), however, it was non-diastereoselective (d.r. 1:1).



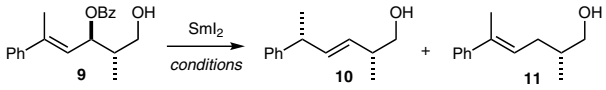
Entry	Additive[a]	7:8[b]	7 d.r.[b]
1.	DMPU	1.3:1	60:40
2.	*t*-BuOH	3:1	69:31
3.	MeOH	3:1	60:40
4.	H_2O	5:1	50:50

Notes:
[a] Reactions were performed by adding the additive (16 equiv DMPU or 1400 equiv ROH) to SmI_2 (7 equiv) followed by the substrate at room temperature.
[b] Determined by NMR

Scheme 3 Initial screening of compound **4** reductions with SmI_2

We surmised that removal of the PMB-protecting group and performing the reaction with a free hydroxyl at this position might impart better diastereoselectivity through enhanced samarium chelation.[14] Indeed after deprotection with DDQ, samarium reduction of the primary alcohol compound **9** now proceeded with not only improved regioselectivity but also enhanced diastereoselectively (up to 76:24). Table 1 presents results from our investigations into the impact of different proton sources on the outcome of the reaction with **9**. Interestingly, the highest (and nearly identical) diastereoselectivities were obtained using either anhydrous conditions followed by quenching (DMPU, entry 1) or in the presence of water (entry 5),[15] suggestive against an internal protonation by the hydroxyl group per se.[16] These reactions produced compound **10** as a 3:1 mixture of diastereomers and exclusively as the *trans* isomer. However, regioselectivity for the DMPU reaction was much lower (2:1 vs 15:1 for H_2O). In an attempt to improve the diastereoselectivity the reaction was also performed at 0 °C, however the colder conditions gave the same d.r. and an erosion of regioselectivity (entry 6).

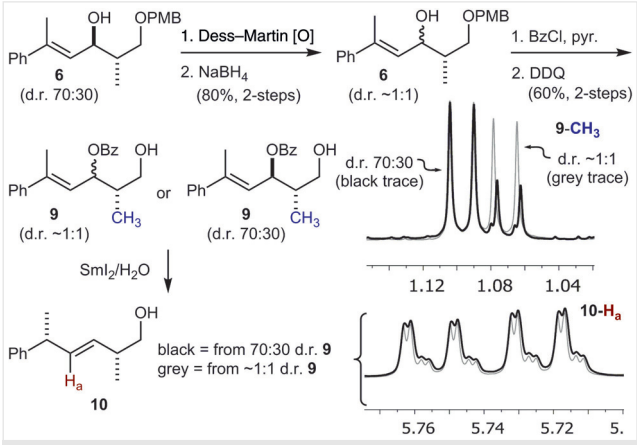
Table 1 Regio- and Diastereoselective Reduction of Alcohol **9**



Entry	Additive[a]	**10**:**11**[b]	Compound **10** d.r.[b]
1	DMPU	2:1	75:25
2	*t*-BuOH	1:0[c]	67:33
3	*i*-PrOH	2.3:1	67:33
4	MeOH	1:0C	60:40
5	H_2O	15:1	76:24
6	H_2O[d]	5:1	75:25

[a] Reactions were performed by adding the additive (16 equiv DMPU or 1400 equiv ROH) to SmI_2 (7 equiv) followed by the substrate and stirring for 30 min.
[b] Determined by NMR.
[c] Compound **11** was not detected by NMR.
[d] The reaction was performed at 0 °C.

In order to determine if the stereochemistry of the OBz stereocenter might impact the stereoselectivity of the reaction, we prepared compound **9** as a ca. 1:1 mixture of diastereomers (compared to the originally obtained ca. 2:1 mixture) using an oxidation/reduction sequence (Scheme 4). As shown, treatment of this 1:1 mixture with SmI_2/H_2O gave product **10** in the same diastereomeric ratio as that obtained when **9** was used as a 70:30 mixture of diastereomers, meaning that there is no memory of chirality associated with the OBz stereocenter.[17] This is attractive from a synthetic standpoint, in that the stereochemistry of this position need not be controlled when preparing substrates for this reaction.

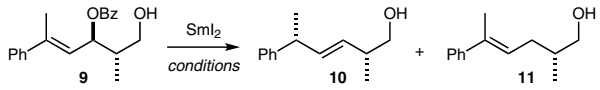


Scheme 4 Examining the impact of compound **9**-OBz stereochemistry on the stereoselectivity of SmI_2-reductions

Table 2 shows optimizations with respect to the equivalents of H_2O for the SmI_2/H_2O reduction of **9**. Interestingly, the d.r. for all of the reactions remained essentially the same, which is in contrast to an earlier report from Keck de-

scribing diastereoselective reductions of β-hydroxyketones by SmI_2 wherein higher equivalents of H_2O leads to a loss of diastereoselectivity.[18] Our results suggest that irrespective of H_2O equivalents, the hydroxyl group in **9** is able to effectively chelate to samarium. This is consistent with other studies showing that even high concentrations of H_2O do not lead to complete saturation of Sm(II).[19] Regioselectivity improved at fewer equivalents of H_2O, perhaps due to minimizing competing intermolecular protonation (*ref.* Scheme 1). Yields also tended to increase with decreased H_2O with the exception of one equivalent, where side products (e.g. possible dimers) were observed leading to a lower isolated yield of **10** (66% with 1 equiv).

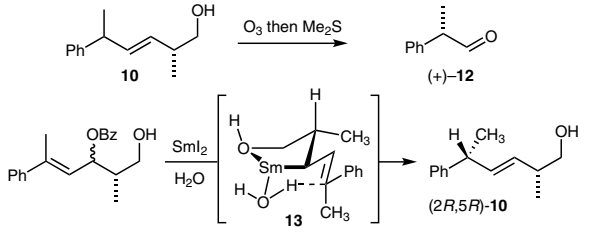
Table 2 Impact of Water Equivalents on Regioselectivity, Diastereoselectivity, and Isolated Yield from the SmI_2 Reduction of Compound **9**[20]



H_2O (equiv)[a]	**10**:**11**[b]	d.r.[b] of **10**	Yield[c] of **10**
200	86:14	75:25	30%
100	86:14	76:24	60%
50	86:14	75:25	75%
25	91:9	75:25	82%
15	97:3	75:25	90%
10	98:2	76:24	76%
5	98:2	72:28	86%
1	100:0	72:28	66%

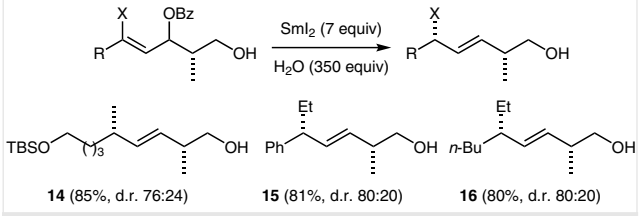
[a] Relative to SmI_2.
[b] Determined by NMR.
[c] Isolated yield.

The stereochemistry of the newly formed stereocenter was determined by ozonolysis of **10** giving aldehyde **12** (Scheme 5). A comparison of the optical activity of **12** to that previously reported[21] revealed that this compound was enriched in the *S*-enantiomer, indicating that the major diastereomer of **10** had the (2*R*,5*R*)-configuration. A potential model that would explain this outcome is given in Scheme 5, based on the energetics of a fused 5,6-bicyclic intermediate **13**,[22] involving hydroxyl chelation of samarium[23] followed by intramolecular protonation by a coordinated water molecule.



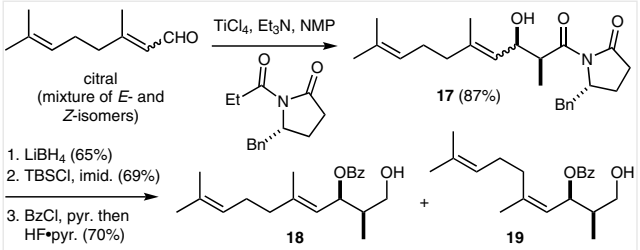
Scheme 5 Determination of absolute stereochemistry of the major stereoisomer of **10** by ozonolysis

The reaction is not limited only to aryl substrates like **9**. For instance, the TBS-protected compound **14** could be obtained with complete regioselectivity and identical diastereoselectivity to that obtained for the phenyl product **10** (ca. 3:1, Scheme 6). At this stage, the stereochemistry of the newly generated methyl stereocenter is assumed to be analogous to compound **10** (*ref.* Scheme 5). Ethyl stereocenters could also be prepared by this protocol using a similar carboalumination (in this case with triethylaluminum)[9] followed by aldehyde addition for substrate preparation. In this way, compounds **15** and **16** ultimately were obtained in 81% and 80% yield, respectively and 4:1 d.r.



Scheme 6 Regio- and diastereoselective SmI_2/H_2O reductions to produce non-aryl and/or non-methyl products **14**–**16**

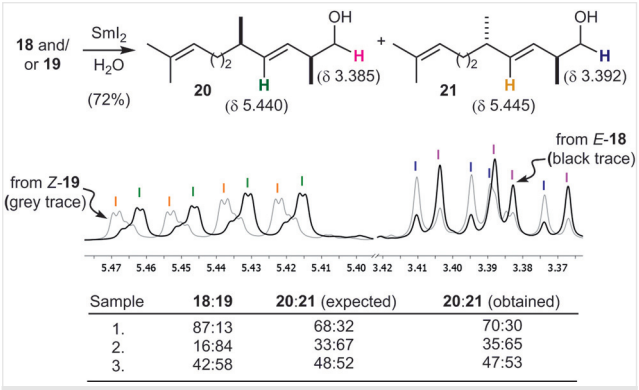
In order to examine the role (if any) of alkene geometry on the stereochemistry of the newly formed stereocenter, we set out to prepare a mixture of (*E*)- and (*Z*)-isomeric substrates. This was accomplished through first an Evans' aldol reaction[24] with citral (mixture of *cis*- and *trans*-isomers) giving *E*/*Z*-**17** (Scheme 7). Reduction with $LiBH_4$, monoprotection of the resulting diol, benzoylation, and removal of the TBS protecting group then produced a mixture of **18** and **19**.



Scheme 7 Synthesis of citral-derived isomers *trans*-**18** and *cis*-**19**

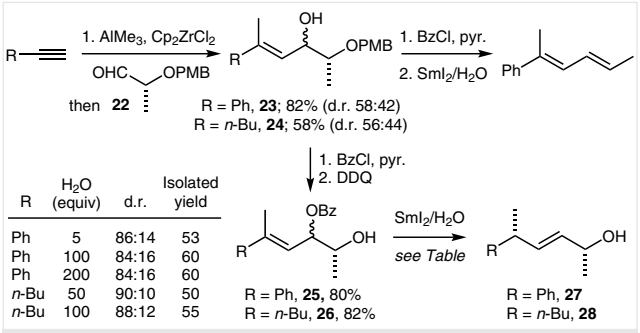
Compounds **18** and **19** were partially separable by chromatography on silica allowing for the isolation of three roughly equal mass fractions: (1) a sample enriched in the *trans*-isomer **18** (87:13 **18**:**19**), (2) a sample enriched in the *cis*-isomer **19** (16:84 **18**:**19**), and (3) a closer to equimolar mixture of **18** and **19** (42:58 **18**:**19**). Each of these mixtures was then taken separately into the reaction with SmI_2/H_2O (Scheme 8). As can be seen from the crude ^1H NMR spectra,

the *cis*- and *trans*-isomers gave opposing selectivities (i.e. major = **20** from **18**; major = **21** from **19**). Using the starting **18**:**19** ratio and anticipated diastereoselectivity based on those previously observed for products **10** and **14** (i.e. 3:1), we could calculate an expected ratio of products **20**:**21** from each of the three samples assuming that the reaction is stereospecific with respect to alkene geometry. As shown, the actual values obtained were very close to those predicted.



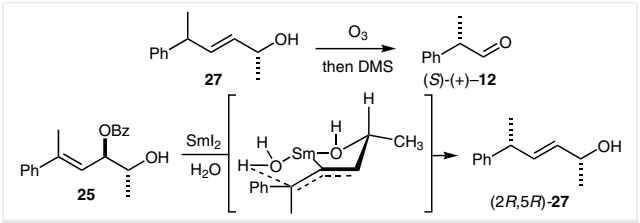
Sample	**18**:**19**	**20**:**21** (expected)	**20**:**21** (obtained)
1.	87:13	68:32	70:30
2.	16:84	33:67	35:65
3.	42:58	48:52	47:53

Scheme 8 Alkene stereospecificity experiments using differentially enriched mixtures of **18** and **19**. Colored lines are signals for the same colored hydrogens.



R	H_2O (equiv)	d.r.	Isolated yield
Ph	5	86:14	53
Ph	100	84:16	60
Ph	200	84:16	60
n-Bu	50	90:10	50
n-Bu	100	88:12	55

Scheme 9 Synthesis and elimination of lactate-derived compounds **23**–**26**



Scheme 10 Ozonolysis and determination of the stereochemistry of the major isomer of compound **27**

We also prepared and investigated the reductive cleavage of lactate aldehyde **22**[25]-derived benzoate esters **23**–**26** (Scheme 9).[26] Perhaps unsurprisingly, treatment of PMB-protected compound **23** with SmI_2/H_2O led exclusively to β-elimination. Removal of the PMB protecting group suppressed this competing process to some extent, allowing for **27** to be obtained in 53% yield from **25** when using five equivalents of water. It was hypothesized that increasing the amount of water might increase the rate of protonation relative to elimination thus improving the yields. Indeed, the use of 100 equivalents of water gave a higher yield (60% vs 53%).[20] Further increasing the amount of water equivalents to 200 equivalents, however, resulted in no additional yield enhancement. The diastereomeric ratios for compounds **27** and **28** were slightly higher (86:14 and 90:10, respectively) than those obtained from the related Roche ester derived compounds (ca. 75:25, see Table 2).

Ozonolysis of product **27** again gave primarily (*S*)-(+)-**12**, indicating that the absolute stereochemistry of the major isomer of **27** was (2*R*,5*R*) (Scheme 10). A possible model for this selectivity is given, similar to that previously proposed for the one-carbon homologated samarium intermediate **13** but as an η^3-complex.[27] At this stage, however, extended hydrogen bonded networks involving multiple water molecules[28] and/or multiple samariums[29] need also be considered.

In sum, SmI_2/H_2O reductions of allylic benzoates adjacent to trisubstituted alkenes and flanked by an alcohol stereocenter occur with high regioselectivity and good diastereoselectivity. The method appears to be quite general in terms of the types of stereocenters (e.g. methyl, ethyl, etc.) that may be installed. Selectivity is proposed to arise through chelation of the hydroxyl group to samarium followed by intramolecular protonation by samarium-coordinated water, with stereochemistry controlled by ring-conformation considerations and starting alkene geometry. Current efforts are aimed at further understanding the mechanism and selectivity of this reaction, as well as exploring alternative auxiliary groups that may afford better diastereoselectivities.

Funding Information

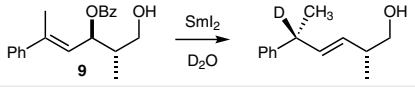
Financial support from the National Science Foundation (CHE-1151492) is gratefully acknowledged.

Supporting Information

Supporting informations for this article is available online at https://doi.org/10.1055/s-0036-1590831.

References and Notes

(1) (a) Nicolaou, K. C.; Ellery, S. P.; Chen, J. S. *Angew. Chem. Int. Ed.* **2009**, *48*, 7140. (b) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371. (c) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 843.
(2) (a) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008. (b) Amiel-Levy, M.; Hoz, S. *J. Am. Chem. Soc.* **2009**, *131*, 8280. (c) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Commun.* **2012**, *48*, 330. (d) Szostak, M.; Spain, M.; Parmar, D.; Procter, D. J. *Chem. Soc. Rev.* **2013**, *42*, 9155. (e) Szostak, M.; Spain, M.; Eberhart, A. J.; Procter, D. J. *J. Org. Chem.* **2014**, *79*, 11988.
(3) Procter, D. J.; Flowers, R. A. II.; Skrydstrup, T. *Organic Synthesis using Samarium Diiodide*; RSC Publishing: Cambridge, UK, **2010**.
(4) Schaefer, S. L.; Roberts, C. L.; Volz, E. O.; Grasso, M. R.; O'Neil, G. W. *Tetrahedron Lett.* **2013**, *54*, 6125.
(5) Yoshida, A.; Hanamoto, T.; Inanaga, J.; Mikami, K. *Tetrahedron Lett.* **1998**, *39*, 1777.
(6) Wright, A. M.; O'Neil, G. W. *Tetrahedron Lett.* **2016**, *57*, 3441.
(7) Takeda, M.; Takatsu, K.; Shintani, R.; Hayashi, T. *J. Org. Chem.* **2014**, *79*, 2354.
(8) Marko, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089.
(9) Wipf, P.; Lim, S. *Angew. Chem. Int. Ed.* **1993**, *32*, 1068.
(10) Mulzer, J.; Mantoulidis, A.; Öhler, E. *J. Org. Chem.* **2000**, *65*, 7456.
(11) (a) Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959**, *81*, 2748. (b) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462.
(12) See Supporting Information.
(13) For another report of SmI_2 dimerization, see: Doisneau, G.; Beau, J.-M. *Tetrahedron Lett.* **1998**, *39*, 3477.
(14) Kawatsura, M.; Hosaka, K.; Matsuda, F.; Shirahama, H. *Synlett* **1995**, 729.
(15) The reaction was also performed using DMPU and H_2O together and gave the same d.r. (75:25) as that obtained when using DMPU (entry 1) or H_2O (entry 5).
(16) Performing the reaction in D_2O resulted in deuterium incorporation at C5 (Scheme 11):



Scheme 11

(17) For a recent review, see: Alezra, V.; Kawabata, T. *Synthesis* **2016**, *48*, 2997.
(18) Keck, G. E.; Wager, C. A.; Sell, T.; Wager, T. T. *J. Org. Chem.* **1999**, *64*, 2172.
(19) Sadasivam, D. V.; Teprovich, J. A. Jr.; Procter, D. A.; Flowers, R. A. *Org. Lett.* **2010**, *12*, 4140.
(20) **General Procedure for SmI_2/H_2O Reductions**: To a solution of SmI_2 in THF (0.1 M, 11.2 mL) was added degassed H_2O (2.0 mL) and the resulting red solution was stirred for 5 min before adding the substrate (0.16 mmol). The solution was stirred for 30 min before quenching with aq $NaHCO_3$ (20 mL) and extracting with EtOAc (2 × 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was then purified by flash column chromatography on silica to yield:
Compound **10**: 20 mg (60%). *Spectral data for the major isomer*: IR (ATR): 3360, 3083, 3061, 3025, 2961, 2925, 2871, 1950, 1876, 1803, 1716, 1601, 1492, 1415, 1373, 1272, 1029, 971, 760, 698 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.38 (t, *J* = 4.7 Hz, 1 H), 7.30 (t, *J* = 6.9 Hz, 2 H), 7.20 (d, *J* = 8.0 Hz, 2 H), 5.74 (ddd, *J* = 15.5, 6.8, 1.1 Hz, 1 H), 5.33 (ddd, *J* = 15.5, 7.9, 1.4 Hz, 1 H), 3.47 (m, 2 H), 3.38 (dd, *J* =10.6, 8.1 Hz, 1 H), 2.36 (hept, *J* = 7.0 Hz, 1 H), 1.36 (d, *J* = 7.0 Hz, 3 H), 1.01 (d, *J* = 6.9 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 146.04, 136.89, 131.00, 128.43, 127.07, 126.06, 67.35, 42.27, 39.66, 21.48, 16.60. HRMS (ESI$^+$): *m*/*z* [M]$^+$ calcd for $C_{13}H_{18}O^+$: 190.1358; found: 190.1358.
Compound **27**: 27 mg (60%). *Spectral data for major diastereomer*: IR (ATR): 3328, 3083, 3060, 3026, 2967, 2925, 2871, 1601, 1493, 1451, 1370, 1274, 1060, 970, 760, 699 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.30 (t, *J* = 7.6 Hz, 2 H), 7.18–7.22 (m, 3 H), 5.82 (ddd, *J* = 15.4, 6.7, 1.1 Hz, 1 H), 5.56 (ddd, *J* = 15.5, 6.6, 1.4 Hz, 1 H), 4.30 (p, *J* = 6.4 Hz, 1 H), 3.46 (p, *J* = 7.0, 6.4 Hz, 1 H), 1.36 (d, *J* = 7.0 Hz, 3 H), 1.28 (d, *J* = 6.4 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 145.56, 135.41, 132.87, 128.44, 127.16, 126.16, 68.87, 41.83, 23.42, 21.17. HRMS (ESI$^+$): *m*/*z* [M – OH]$^+$ calcd for $C_{12}H_{15}$: 159.1174; found: 159.1175.
(21) Corey, E. J.; Hannon, F. J.; Boaz, N. W. *Tetrahedron* **1989**, *45*, 545.
(22) Eleil, E. L.; Pillar, C. *J. Am. Chem. Soc.* **1955**, *77*, 3600.
(23) Prasad, E.; Flowers, R. A. II. *J. Am. Chem. Soc.* **2002**, *124*, 6357.
(24) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.
(25) Yu, W.; Zhang, Y.; Jin, Z. *Org. Lett.* **2001**, *3*, 1447.
(26) Qi, W.; McIntosh, M. C. *Org. Lett.* **2008**, *10*, 357.
(27) Bied, C.; Kagan, H. B. *Tetrahedron* **1992**, *48*, 3877.
(28) Chciuk, T. V.; Anderson, W. R. Jr; Flowers, R. A. *J. Am. Chem. Soc.* **2016**, *138*, 8738.
(29) Prasad, E.; Flowers, R. A. *J. Org. Chem.* **2005**, *127*, 18093.