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Journal
Angewandte Chemie, 59(40)

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Publication Date
2020-09-28

DOI
10.1002/anie.202005267

Peer reviewed

HHS Public Access

Author manuscript

Angew Chem Int Ed Engl. Author manuscript; available in PMC 2021 June 25.

Published in final edited form as:

Angew Chem Int Ed Engl. 2020 September 28; 59(40): 17565–17571. doi:10.1002/anie.202005267.

Dealkenylative Alkenylation: Formal σ-Bond Metathesis of Olefins

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Abstract

The dealkenylative alkenylation of alkene C(sp^3)–C(sp^2) bonds has been an unexplored area for C–C bond formation. Herein 64 examples of β-alkylated styrene derivatives, synthesized through the reactions of readily accessible feedstock olefins with β-nitrostyrenes by ozone/Fe^{II}-mediated radical substitutions, are reported. These reactions proceed with good efficiencies and high stereoselectivities under mild reaction conditions and tolerate an array of functional groups. Also demonstrated is the applicability of the strategy through several synthetic transformations of the products, as well as the syntheses of the natural product iso-moracin and the drug (E)-metanicotine.

Keywords

alkenes; ozonolysis; radicals; redox chemistry; terpenoids

Introduction

Alkenes are seemingly ubiquitous functionalities in the library of organic molecules, and they play hugely important roles in chemical science, organic synthesis,[1] the functionalization of bio-active molecules, and materials synthesis[2] Furthermore, olefins are the second most frequently encountered functional group in natural products (39.85 %) and are also readily available from petroleum,[3] so the development of new modalities for synthesizing alkenes directly from feedstock alkenes would presumably benefit the scientific community. Seminal examples of alkene-to-alkene conversions, including olefin metathesis[4] and the Heck reaction,[5] complement the more traditional Wittig reaction[6] and alkyne semi-reduction.[7] In addition, Heck-type alkenylations[8] and carbonyl–olefin metathesis[9] have emerged as alternative platforms for olefin synthesis in recent years (Scheme 1 A).

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Conflict of interest

The authors declare no conflict of interest.

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.202005267.

Radicals play significant roles in many chemical transformations[10] One of the important methods for accessing olefin-derived alkyl radicals[11] relies upon pioneering studies on iron-mediated decomposition of α-alkoxy hydroperoxides.[12,13] Continuing our interest in the dealkenylative functionalization of alkenes through ozone/Fe^{II}-mediated $C(sp^3)$–$C(sp^2)$ bond fragmentation,[14] we envisioned trapping their alkyl radical intermediates through addition-elimination onto olefins. When implemented, this dealkenylative alkenylation could, for example, employ feedstock alkenes (e.g., terpenes, terpenoids) in conjunction with alkenes containing an open-shell leaving group. This approach could also be an attractive option for the synthesis and functionalization of a new class of terpenoid-tethered alkenes. To the best of our knowledge, there are no previous examples of dealkenylative approaches for generating alkyl radical intermediates for the synthesis of functionalized olefins.

The process we propose herein involves Criegee ozonolysis[15] of an alkene **I** in MeOH followed by Fe^{II}-mediated fragmentation of the resulting α-methoxy hydroperoxide **II**, β-scission of the alkoxy radical to generate the alkyl radical **III**, radical addition with an alkenylating agent to give the intermediate **IV**, and β-elimination giving the (*E*)-alkenylated product **V** (Scheme 1B). Most notably, this method is a complementary procedure for the synthesis of β-alkylated styrenes-important structural units in many natural products, bioactive molecules, and pharmaceuticals, including metanicotine, vorapaxar, and tamoxifen (Scheme 1C).[16,17]

Results and Discussion

We commenced our investigation by reacting (−)-isopulegol (**1a**) as a model alkene with a range of structurally diverse vinylation agents: (*E*)-(2-bromovinyl)benzene (**2**),[18] cinnamic acid (**3**),[19] two β-nitrostyrenes **4**,[20] (E)-[2-(benzenesulfonyl)vinyl]benzene (**5**),[21] (*E*)-1-styryl-1,2-benziodoxol-3(1*H*)-one (**6**)[22] (entries 1–6, Table 1). Among them, 4-methyl-β-nitrostyrene (**4b**) performed the best, providing the desired styrylated cyclohexanol **7ab** in 47 % yield (entry 4). The byproducts associated with the reaction were the alkene **7a′** and the ketone **7a′′**, as well as a trace amount of the radical homocoupling product **7a′′′**, which was detected using liquid chromatography mass spectrometry (LCMS) (see the Supporting Information for further discussion). Among various iron salts tested, $FeSO_4{\cdot}7\mathbf{H}_2O$ proved to be the most efficient in promoting the desired alkenylation. Other transition metal salts known to facilitate the decomposition of hydroperoxides,[23] including $MnSO_4{\cdot}x\mathbf{H}_2O$, $CoSO_4{\cdot}7\mathbf{H}_2O$, $VOSO_4$, and $TiCl_3$, were ineffective at delivering the desired product **7aa** (entries 7–9). Screening of solvents revealed that MeOH was crucial for the reaction. Additional efforts at optimizing the reaction conditions using co-solvents, excess of radical acceptor, and additives failed to offer better results. A promising yield of **7ab** (71%) with high diastereoselectivity (10:1 d.r.) was obtained when performing the reaction with 2.2 equivalents of the alkene and 1.5 equivalents of $FeSO_4{\cdot}7\mathbf{H}_2O$ at 0 °C (entry 11). Further lowering the reaction temperature to −20 °C diminished the yield of **7ab**, presumably because of the poor solubility of **4b** in MeOH at this temperature (entry 12).

We applied the conditions optimized for deisopropenylative styrylation of (−)-isopulegol (**1a**) to other terpenoids and their derivatives (Scheme 2). The dealkenylative alkenylations

of **1a** in conjunction with 4-methoxy-β-nitrostyrene (**4e**) and 4-bromo-β-nitrostyrene (**4i**) provided their expected products **7ae** and **7ai** in yields of 78 and 68%, respectively. The (−)-isopulegol-derived methyl ether **1b** afforded the product **7bb** in 72 % yield. Other monoterpenoids, including *trans*-(+)-dihydrocarvone (**1c**) and (−)-dihydrocarveol (**1d**), were also viable substrates, producing their corresponding products **7cb** and **7db** in yields of 72 and 69%, respectively. *cis*-(−)-Limonene oxide (**1e**) underwent opening of the epoxide, through methanolysis, to afford the (*E*)-alkenylated product **7eb** in 55% yield, consistent with our previous finding.[14b] The diterpenoid (+)-nootkatone (**1 f**) also underwent fragmentation cleanly to give the alkenylated product **7fb** in 50% yield. Betulin (**1g**), a biologically active triterpenoid,[24] afforded the desired product **7ga** in a relatively low yield of 32 %, while the protected dehydroleucine **1h** delivered the strylated α-amino acid derivative **7ha** in 38% yield. The carvone-derived cyclopentanol **1i** also gave the ester **7ib** in 57 % yield. Two other terpenoid-derived substrates, the dihydrocarvone-derived hydroxy ketone **1j** and the enone **1k**, provided their respective products **7jb** (70%) and **7kb** (62%). The stereoselectivity of the radical addition was dictated by a combination of torsional and steric strain induced by the substituents at the α-, β-, and γ-positions of the alkene substrate.[25] To expand the scope of olefin coupling partner, we tested other readily accessible alkenes. Expectedly, both isopropenyl- and β-styrylcyclohexane provided the desired product **7lb** in 76 and 74 % yield, respectively. We found that all degrees of alkyl radicals (1°, 2°, and 3°) engaged efficiently in the dealkenylative alkenylation, generating their corresponding products in moderate to good yields (**7lb**-**7zb**, 30–76%). In contrast, the benzylic radical precursor **1aa** failed to deliver the desired product **7aab** under our standard reaction conditions (see the Supporting Information for other incompatible substrates). Notably, a variety of commonly encountered functionalities, including hydroxy, ketone, ester, amide, enone, carbamate, and phthalimide units, were compatible with the reaction conditions.

Next, we examined the scope of the nitroolefin coupling partners for reactions with the alkene **1l** (Scheme 3). Nitrostyrenes bearing a variety of substituents on the benzene ring (**4c**–**4n**), thiophene (**4o**), naphthalene (**4p**), and benzodioxole (**4q**) were compatible, giving their corresponding alkenylated products **7lc**–**7lq** in yields of 42–78 %. Several functional groups, including hydroxy (**4h**), halide (**4i**-**4l**), nitro (**4 m**), and trifluoromethyl (**4n**) units, were tolerated. Notably, the β,β-disubstituted nitroolefins **4r** and **4s** generated the trisubstituted olefins **7lr** and **7ls** in 64 and 70 % yield, respectively. In contrast, when the α-methylated nitroolefin **4t** was used as substrate, the desired product **7lt** was not observed, presumably because its steric bulk hindered addition of the cyclohexyl radical at the α-carbon atom. The β-alkyl-substituted nitroolefins (**4u** and **4v**), as well as β-dimethylamino-(**4w**) and β-styryl-nitroolefins (**4x**) failed to afford their desired products **7lu**-**7lx**, under these reaction conditions. Notably, this dealkenylative alkenylation proceeded with excellent stereoselectivity, producing only *E*-isomers in most cases.

We broadened the substrate scope by converting the exomethylene cycloalkanes **8** and cycloalkenes **9** into their corresponding alkenyl methyl esters **10** and aldehydes **11**, respectively (Scheme 4). The simple exomethylene cycloalkanes **8a**–**8c** gave their styrylated esters **10ab**–**10cb** in yields of 58–67 %. 1-Methylene indane (**8d**) afforded 41 % of its

styrylated product **10db**, while 1-methylene tetralin (**8e**) gave the product **10eb** in 21% yield. Camphene (**8f**) and sabinene (**8g**) fragmented to give their corresponding esters **10fb** and **10gb** in moderate yields (32 and 45 %, respectively). The cycloalkenes **9a** and **9b** also underwent the reaction smoothly, affording their styrylated aldehydes in yields of 51 and 60%, respectively. Remarkably, we could access the aldehyde **11ab**–an intermediate for the synthesis of cyclopenta[*b*]quinoline and taxol-like tricyclic derivatives that has previously been made over five steps in 41 % yield[26]–in a single step in 51 % yield. (+)-*p*-1-Menthene (**9c**) also reacted to generate the desired aldehyde **11cb** in 56 % yield. The disubstituted olefins norbornene (**9d**) and *cis*-cyclooctadiene (**9e**) produced their respective aldehydes **11db** (53%) and **11eb** (41%). Dealkenylative cleavage of (+)-2-carene (**9f**) produced the aldehyde **11fb** in 51 % yield. Finally, the reaction of (*1S*)-(+)-3-carene (**9g**) gave the dienyl-aldehyde product **11ge**, isolated in 45 % yield, through a radical-induced ring opening process of the transient cyclopropylcarbinyl radical.

In addition to the radical ring opening test, we conducted several control experiments to support the involvement of radical intermediates (Scheme 5). The addition of 1.5 equivalents of TEMPO, under our standard conditions, inhibited the alkenylation of **1j** with **4b**, yielding only 12% of the desired product along with the TEMPO-alkyl adduct in 74 % yield with 4:1 d.r. The alkenylation was stereoconvergent, with both *trans*- and *cis*-β-nitrostyrenes yielding the *trans*-(*E*)-alkenylated product **7aa** exclusively with the same *E*/*Z* ratio.

To validate the practicality and generality of this transformation, we performed a gram-scale reaction employing 20 mmol of (−)-isopulegol (**1a**) and obtained the desired styrylated cyclohexanol **7ab** in a yield of 57% (1.12 g) and with 10:1 d.r. (Scheme 6A). Furthermore, the operational simplicity of this ozone/Fe^{II}-mediated process encouraged us to explore its synthetic utility by performing various post-alkenylation transformations and by synthesizing a natural product and a known pharmaceutical drug (Schemes 6B–D). Ozonolysis and reductive workup of the dealkenylative product **7ab** gave the chiral cyclohexanediol **13** in 59 % yield. Hydrogenation of the product **7ab** furnished the enantiopure cyclohexanol **14** in almost quantitative yield (95%). β-Chlorotetrahydrofuran derivatives are important motifs in several natural products.[27] We converted the alkene **7ab** to the enantiopure tetrahydrofuran **15** in 82 % yield. This reaction, proceeding via a 5-*endo*-chlorocycloetherification, could serve as a convenient strategy for the synthesis of various tetrahydrofuran derivatives.[28] A cascade reaction generating the octahydroindenobenzofuran **16** was achieved in an excellent yield of 75 % through selective Prins cyclization followed by Friedel-Craft cyclization when reacting the strylated cyclohexanol **7ai** and 3,4,5-trimethoxybenzaldehyde with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at room temperature.[29] These post functionalized products containing multiple stereocenters, obtained from readily accessible starting materials, could find potential applications in organic synthesis.

We have also completed a formal synthesis of isomoracin C (**17**),[30] a 2-arylbenzo[*b*]furan from the *Artocarpus* family that has potent 5-lipooxygenase inhibitory activity [IC_{50} (5LOX) = 1.67 μM]. The known precursor **7ry** was obtained in 56 % yield from the dealkenylative alkenylation of the commercially available alkene **1r** with the nitroolefin **4y**; the synthesis of

7ry was achieved previously in 23 % yield in three steps staring from 3,5-dimethoxybromobenzene.[31] Finally, we have achieved the synthesis of the drug (*E*)-metanicotine (**19**), commonly known as rivanicline, developed originally as a potential treatment for Alzheimer's disease.[32,33] The dealkenylative alkenylation of the alkene **18** with the nitroolefin **4z** proceeded smoothly to afford the intermediate **18z**, which, upon work-up and direct subjection to deprotection with 6N HCl, afforded the drug **19** in an overall yield of 37% with excellent selectivity (*E*/*Z* > 20:1, Scheme 6D).

Conclusion

In summary, we describe a simple and straightforward ozone/Fe^{II}-mediated dealkenylative alkenylation that proceeds under mild reaction conditions in less than 10 min. This transformation is stereoselective and tolerant of a broad range of functionalities. Several natural products and readily accessible alkenes react with an array of nitroolefins to give pharmaceutically relevant and synthetically important alkylated styrenes. This protocol also provides a useful synthetic route toward styrenes presenting tethered aldehydes and esters. We have also demonstrated the utility of the products through various post-alkenylation transformations, synthetic applications, and the diversification of natural products. In view of the mild experimental conditions and the ready availability of both the reaction partners and the inexpensive earth-abundant reagents, this convenient and site-specific alkenylation should find practical applications in chemical science.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Financial support for this study was provided by the NIH (R01GM071779). We thank the UCLA Molecular Instrumentation Center for the NMR spectroscopy and mass spectrometry instrumentation and the X-ray diffraction studies (S. I. Khan). We thank Andrew J. Smaligo for his assistance with the preparation of the figures and the recording of 2D NMR spectra.

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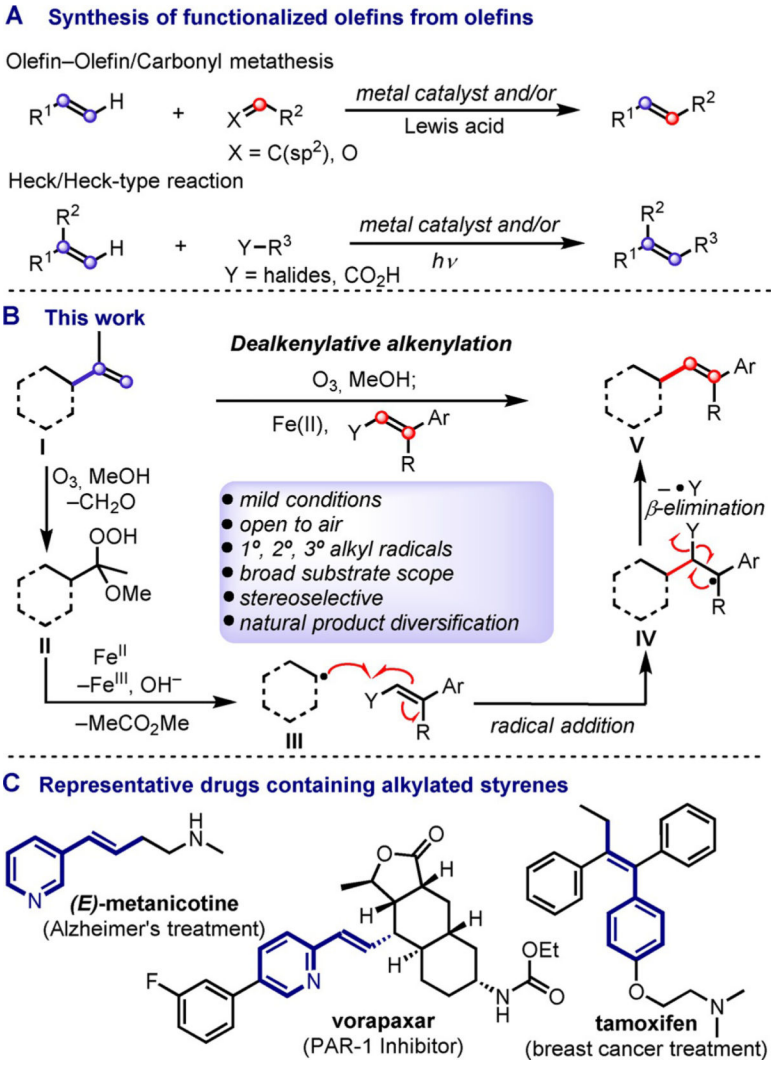
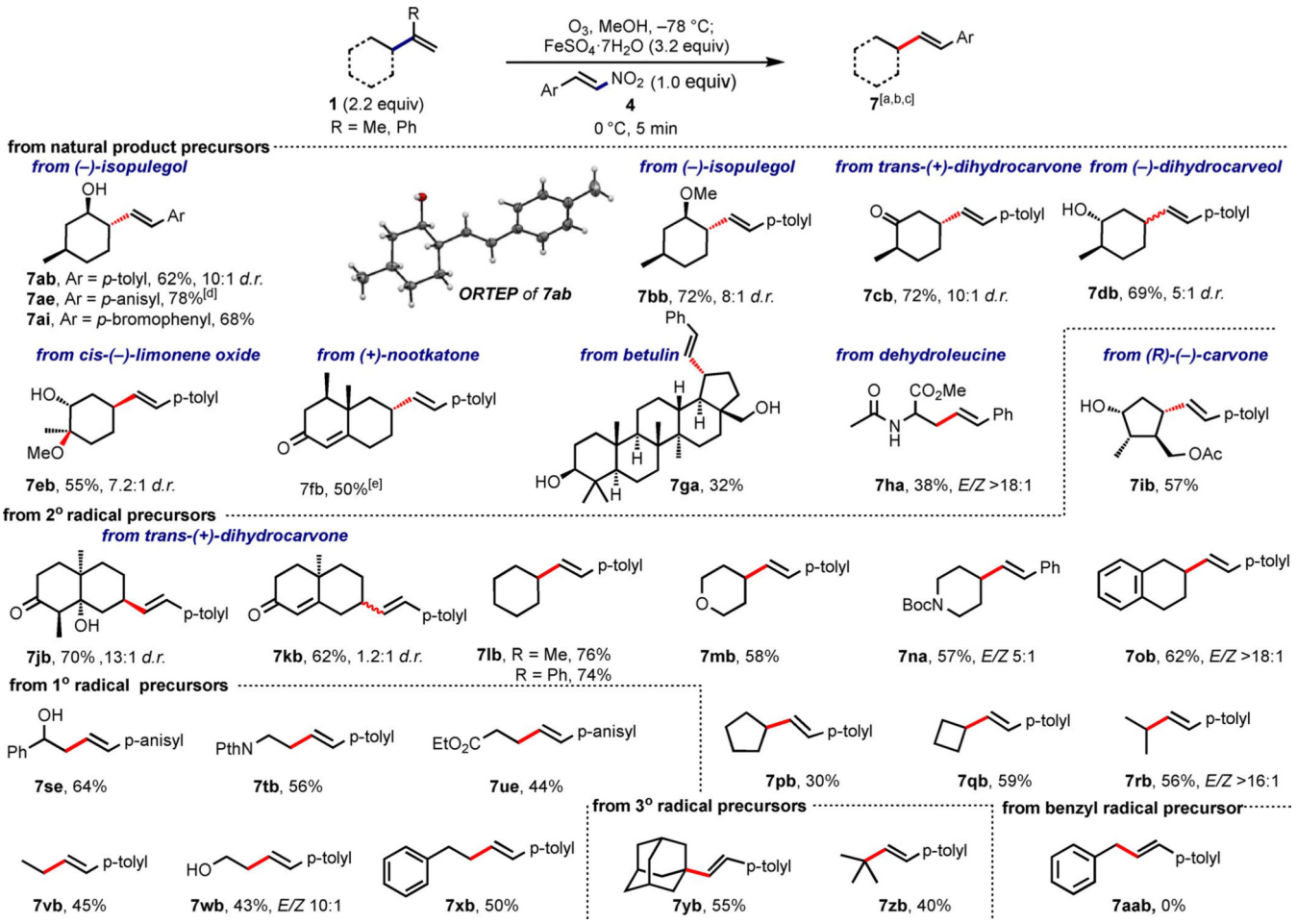
[34]. CCDC 1986086 (7ab) and 1986087 (16) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.



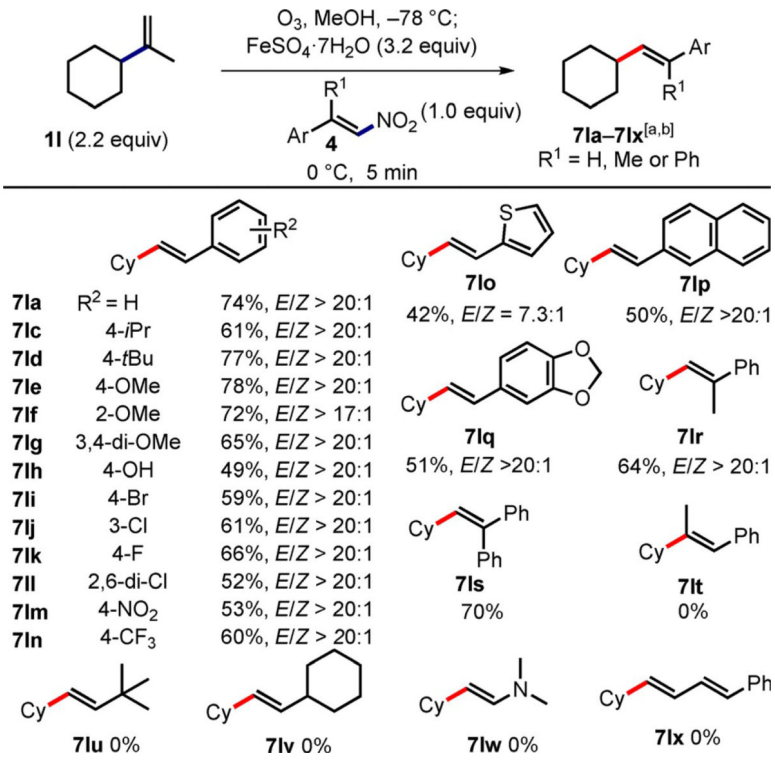
Scheme 1.

A) Known transformations of olefins Into functionalized olefins. B) Dealkenylative alkenylation presented herein. C) Structures of three examples of styrene-containing drugs.



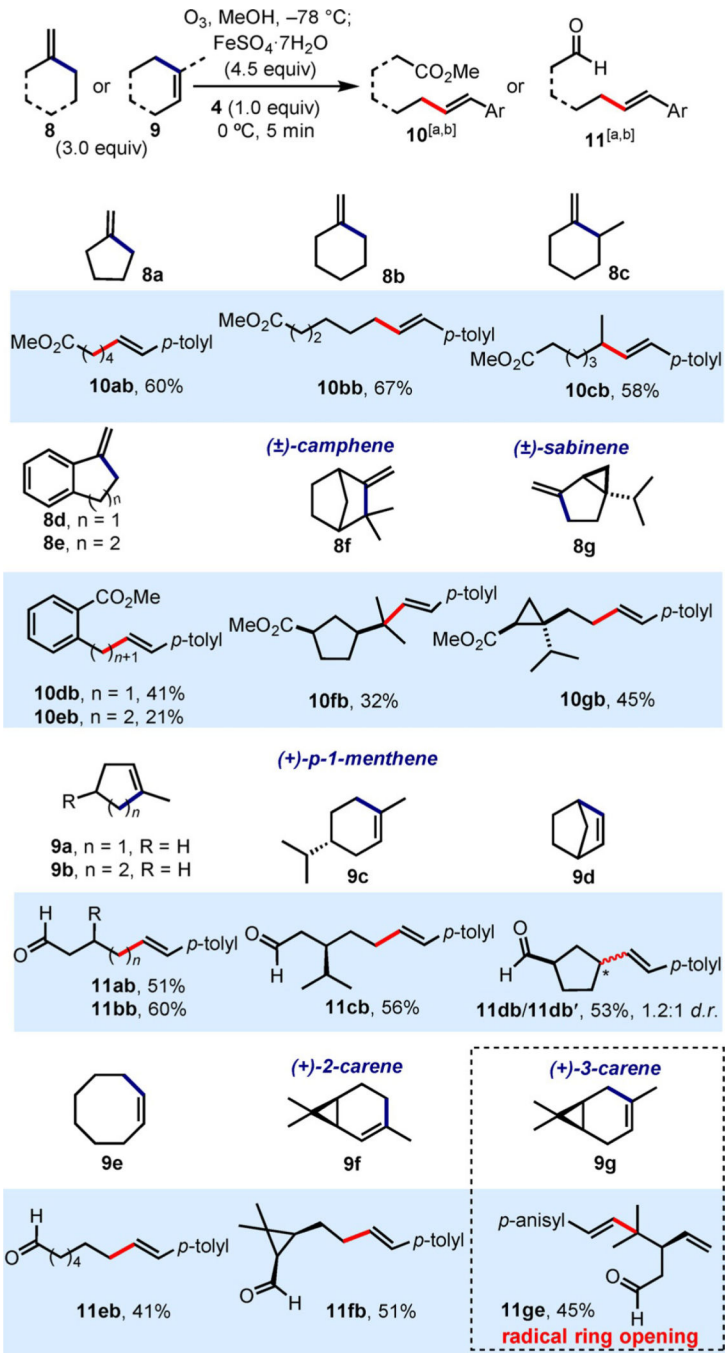
Scheme 2.

Scope of alkene coupling partner in reactions with nitroolefins **4**. The X-ray structure of **7ab** is shown.[34] [a] Nitroolefin (0.46 mmol), alkene (1.0 mmol), $FeSO_4 \cdot 7H_2O$ (1.50 mmol), MeOH (0.025 M), 0°C, 5 min. [b] Unless otherwise stated, the *E/Z* ratio was >20:1 and the *d.r.* ratio was calculated from the ^1H NMR spectrum of the crude product or the isolated products of the major and minor isomers. [c] Yield of isolated product. [d] The reaction was performed on a 5.00 mmol scale. [e] The reaction was performed at room temperature.



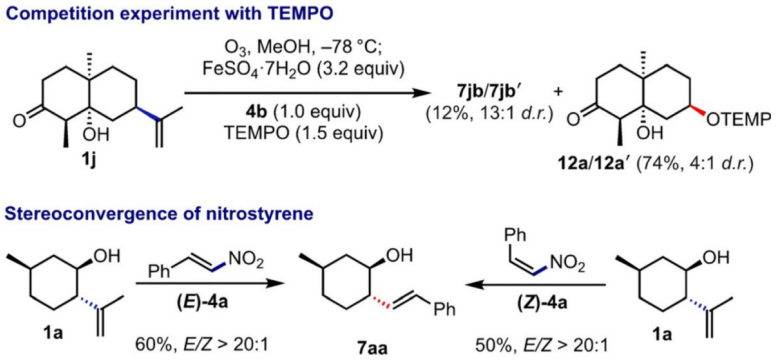
Scheme 3.

Substrate scope of the reactions of **1 l** with various nitroolefins **4**. [a] Standard conditions: nitroolefin **4** (0.46 mmol), alkene **1 l** (1.00 mmol), $FeSO_4{\cdot}7\mathbf{H}_2O$ (1.50 mmol), MeOH (0.025 M with respect to **1 l**), 0°C, 5 min. [b] Yield of isolated product.



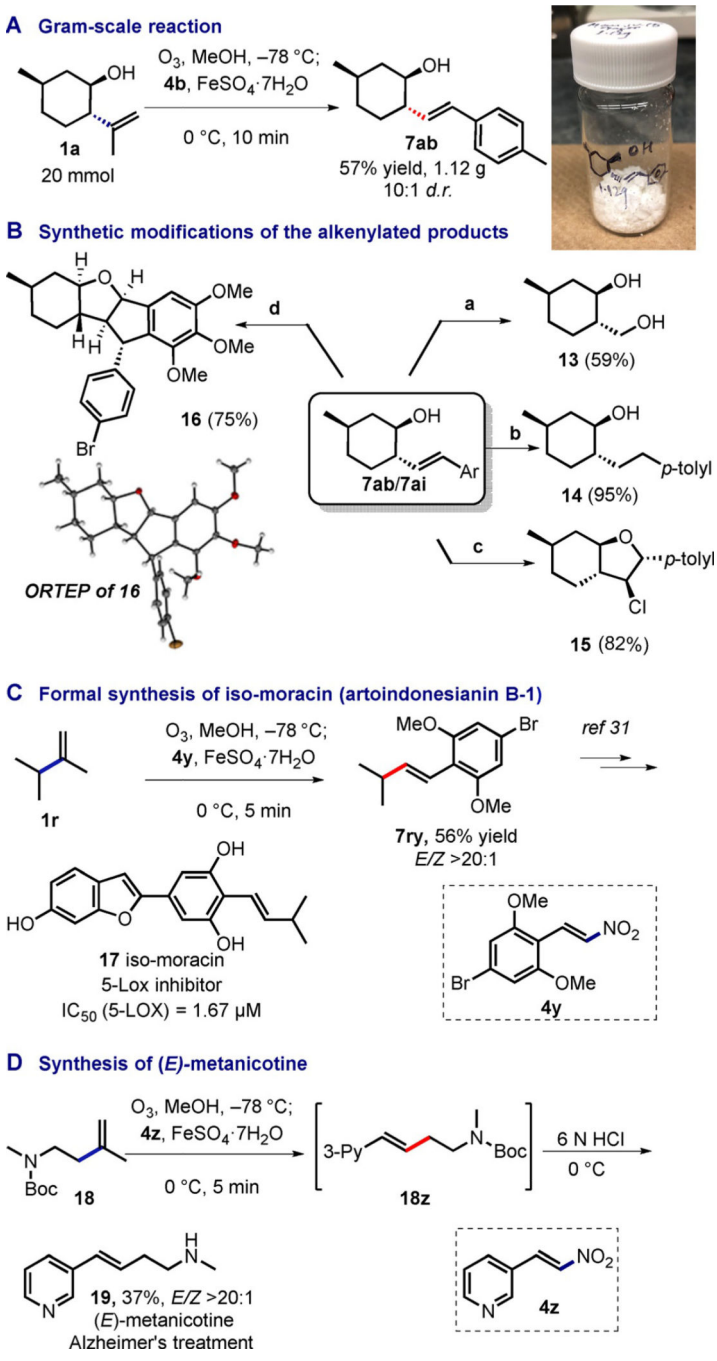
Scheme 4.

Substrate scope for the reactions of exocyclic and endocyclic olefins. [a] Nitroolefin (0.33 mmol), alkene (1.00 mmol), $FeSO_4{\cdot}7\mathbf{H}_2O$ (1.50 mmol), MeOH (0.025 M with respect to the alkene), 0°C, 5 min. Unless otherwise stated, the *E*/*Z* ratio was >20:1 and the d.r. ratio was calculated from the ^{1}H NMR spectrum of the crude product. [b] Yield of the isolated product.



Scheme 5.

Reactions conducted to examine mechanistic features of the dealkenylative alkenylation. See the Supporting Information for details.

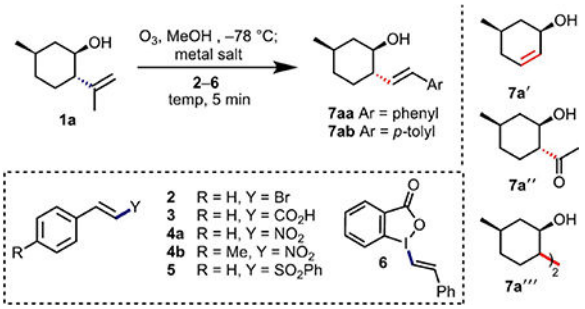


Scheme 6.

Synthetic utility and applications of the dealkenylative alkenylation. The X-ray structure of **16** is shown.[34] [a] Unless otherwise noted, yields are those of isolated products. See the Supporting Information for experimental details. [b] *E*/*Z* ratios were determined from ^{1}HNMR spectra. [c] Conditions: a) O_3, CH_2Cl_2, −78°C, $NaBH_4$ (excess), 1 h. b) Pd/C, H_2, EtOH, rt, 8 h. c) SO_2CI_2, CH_2Cl_2, 0°C, 15 min. d) 3,4,5-Trimethoxy benzaldehyde, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 45 min.

Table 1:

Optimization of conditions for the reaction of **1a** with selected olefins.[a]



Entry	1a (equiv)	2–6 (equiv)	Metal salt (equiv)	Conc. [m]	*T* [°C]	Yield [%][b,c] 7aa/7ab (d.r.)
1	1.0	**2** (1.5)	$FeSO_4{\cdot}7H_2O$ (1.2)	0.05	rt	13 (7:1)
2	1.0	**3** (1.5)	$FeSO_4{\cdot}7H_2O$ (1.2)	0.05	rt	10 (13:1)
3	1.0	**4a** (1.5)	$FeSO_4{\cdot}7H_2O$ (1.2)	0.05	rt	41 (10:1)
4	1.0	**4b** (1.5)	$FeSO_4{\cdot}7H_2O$ (1.2)	0.05	rt	47 (10:1)
5	1.0	**5** (1.5)	$FeSO_4{\cdot}7H_2O$ (1.2)	0.05	rt	18 (8:1)
6	1.0	**6** (1.5)	$FeSO_4{\cdot}7H_2O$ (1.2)	0.05	rt	22 (10:1)
7	1.0	**4a** (1.5)	$MnSO_2{\cdot}xH_2O$ (1.2)	0.05	rt	–
8	1.0	**4a** (1.5)	$CoSO_4{\cdot}7H_2O$ (1.2)	0.05	rt	–
9	1.0	**4a** (1.5)	$TiCl_3$ (1.2)	0.05	rt	–
10	2.2	**4b** (1.0)	$FeSO_4{\cdot}7H_2O$ (1.5)	0.025	rt	65 (10:1)
11[d]	2.2	**4b** (1.0)	$FeSO_4{\cdot}7H_2O$ (1.5)	0.025	0	71 (10:1)
12	2.2	**4b** (1.0)	$FeSO_4{\cdot}7H_2O$ (1.5)	0.025	−20	42 (8:1)

[a] Reaction performed on 0.05-mmol scale

[b] Yield determined using ^{1}H NMR spectroscopy with 1-chloro-2,4-dinitrobenzene as internal standard (*d.r.* in parentheses)

[c] Unless stated otherwise, *E/Z* ratio was >20:1, calculated from ^{1}H NMR spectrum of crude product.

[d] Yield of isolated product was 62%. See the Supporting Information for detailed procedures.