Catalytic Allylic Oxidation of Alkenes Using an Asymmetric Kharasch–Sosnovsky Reaction

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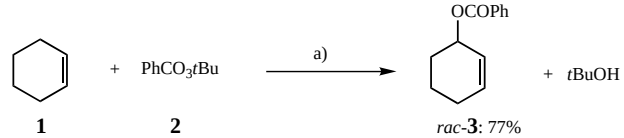
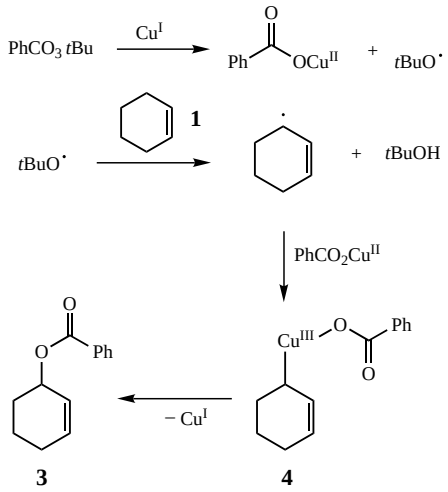
Abstract: Kharasch and Sosnovsky reported the allylic oxidation of alkenes to give racemic allylic benzoates. This could be achieved efficiently using a *tert*-butyl perester as the oxidant, in the presence of a copper or cobalt salt. The use of C_2-symmetric bis(oxazoline) ligands in the presence of copper(I) triflate with cyclic olefinic substrates gave the first synthetically useful asymmetric variant. The enantioselective control was good (up to 84% *ee*) although yields were variable. In all cases the facial preference of the newly formed C–O bond was the same giving an *S* configuration at the allylic stereocenter. Lower stereocontrol was observed for large-ring alkenes and substantially reduced enantioselectivities were found with open-chain alkenes. This reaction has been further screened using a variety bis(oxazoline) and proline-derived ligands, which give a direct correlation between the chirality of the ligand and the enantioselectivity obtained. Individual substrates were found to be extremely sensitive to both the ligand structure and copper salt used as well as the presence of additives such as zinc, hydrazine, and molecular sieves.

Some of the recent developments in the asymmetric allylic oxidation of alkenes have stemmed from a seminal report by Kharasch and Sosnovsky in the late 1950s.[1] They originally showed that allylic oxidation of alkenes, such as cyclohexene (**1**), could efficiently occur using a *tert*-butyl perester **2** as the oxidant, in the presence of a copper or cobalt salt to give allylic benzoates in good yield (Scheme 1). In most cases, the reaction was more efficient using a copper salt. It was proposed that the reaction occurred via a radical mechanism, which was suggested to proceed in a concerted manner, with the copper center being intimately involved in the C–O bond forming step through the allyl cuprate, **4** (Scheme 2).[1] When



Scheme 1. The Kharasch-Sosnovsky reaction: a) cupric 2-ethylhexoate or CuBr, 80 °C, benzene.



Scheme 2. Proposed mechanism for the allylic oxidation of **1**.

the reaction was performed in the presence of an aliphatic acid, the ester of this acid was obtained rather than the corresponding benzoate.

In view of the potential utility of such a synthetic transformation, it does seem remarkable that the first synthetically useful asymmetric variant was only reported in the mid 1990s, independently by the groups of Pfaltz,[2] Andrus,[3] and Katsuki.[4] Pfaltz[2] and Andrus[3] and their co-workers both employed the same series of enantiomerically pure C_2-symmetric bis(oxazoline) groups (**5a–e**) as the ligand in the presence of copper(I) triflate with cyclic olefinic substrates (Scheme 3). The enantioselective control was generally good (up to 84% *ee*) although yields were somewhat more variable. In all cases the facial preference of the newly formed C–O bond was the same, giving an *S* configuration at the newly formed allylic stereocenter. It was clear from these initial studies that a small change in the substituent R^2 (incorporated to prevent oxidation adjacent to the oxygen atom to improve catalyst stability) had a dramatic effect on the resulting

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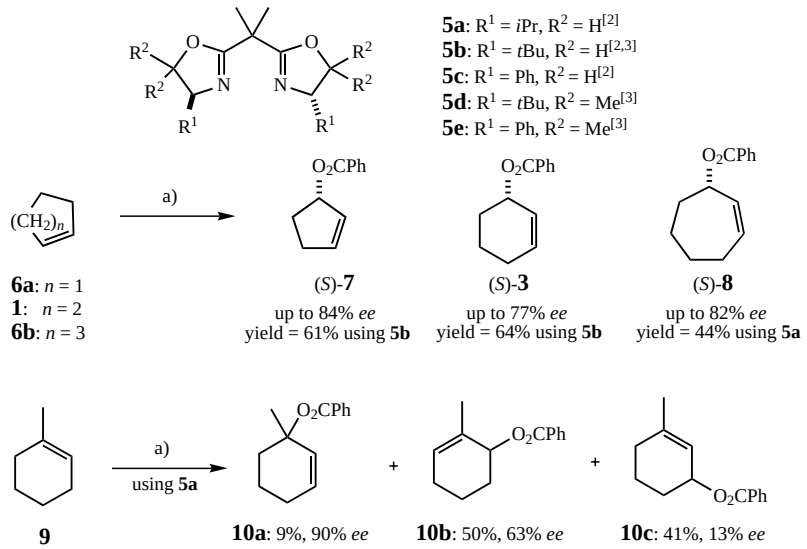
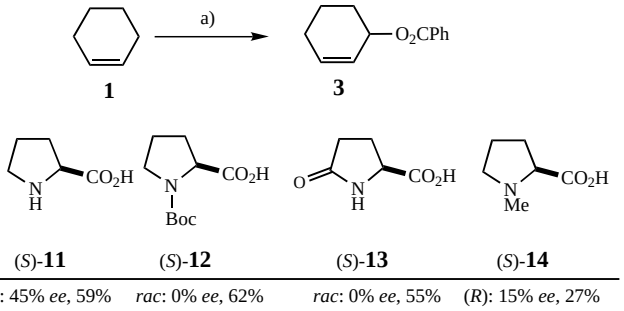


Scheme 3. Allylic oxidation of cycloalkenes using a C_2-symmetric bis(oxazoline) ligand **5**: a) $PhCO_3tBu$, CuOTf (5 mol%), chiral ligand **5a–e** (6–8 mol%); OTf = trifluoromethanesulfonate.

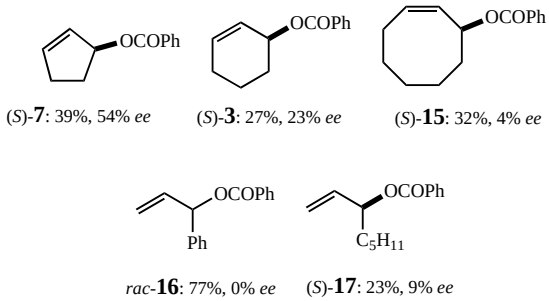
stereocontrol; for example, changing from oxazoline **5b** to **5d** resulted in the enantioselectivity dropping from 70 to 42% *ee* for the synthesis of benzoate **7**. Unfortunately there was no clear pattern to indicate which oxazoline-based ligand would give superior control over a wide range of cycloalkenes, and consequently systematic screening appeared to be the best method of choosing a particular catalyst for a given alkene. High levels of enantioselectivity were obtained for simple cyclopentene, cyclohexene, and cycloheptene rings. However, for larger rings such as cyclooctene, little stereocontrol was observed. Andrus also examined the allylic oxidation of two open-chain alkenes (allylbenzene and 1-octene) and found that although the facial preference was no different than for the cyclic cases, the enantioselectivity was substantially lower. Surprisingly for these substrates, higher levels of enantioselectivity were obtained at higher temperature. Pfaltz further investigated the regioselectivity of this process by allylic oxidation of 1-methylcyclohexene (**9**) and found as expected the formation of a secondary radical was preferred. However, the regiocontrol was rather poor leading to a regioisomeric mixture of benzoates **10a–c** with moderate to good enantioselectivity (Scheme 3).

Some success was also reported for proline and proline derived ligands.[5–7] Muzart and co-workers probed the activity of a series of copper(I) catalysts with proline **11** or proline-like ligands **12–14** for the oxidation of cyclohexene (**1**). They have clearly shown that there is a correlation between the coordinating ability of the chiral ligand (to the copper atom) and the enantioselectivity observed. By lowering the σ-donor ability of the nitrogen atom through delocalization (into either an *exo*- or *endo*-carbonyl group) in **12** and **13**, the facial selectivity was lost (Scheme 4). The use of **14**, the simple *N*-methylated derivative of (*S*)-proline, resulted in the return of some facial control, although rather intriguingly this was in the opposite sense to the natural amino acid **11**. A series of cyclic and acyclic alkenes were systematically screened against the optimum conditions found for **11**, as the chiral ligand. In keeping with the findings of the Pfaltz and Andrus groups it was found that the more conformationally rigid the alkene the better the stereocontrol. Consequently cyclic alkenes gave better control than open-chain alkenes (Scheme 5). Further investigations into the rate of addition of the perester to the reaction mixture and the nature of the active catalyst indicated that a CuL_2 complex was largely responsible for the activity and optimum conditions were found to require the oxidant, $PhCO_3tBu$, to be added in a single portion.[5] Investigations were also made into the effect of the structural nature and acidity of the capturing carboxylic acid (RCO_2H). For strong organic acids, such as CF_3CO_2H no oxidation occurred, whereas sterically demanding acids such as pivalic acid (R = *t*Bu), did provide the highest levels of asymmetric induction (52% *ee*) albeit with very low yield (6.5%).



Scheme 4. Yield and enantioselectivity in the production of **3** by the allylic oxidation of **1** using proline-based ligands **11–14**. a) Cu_2O (2 mol%), chiral ligand **11–14**, $PhCO_3tBu$ (70% aq.); Boc = *tert*-butoxycarbonyl.

Feringa and co-workers have investigated the use of substituted proline variants on this oxidation procedure using **1** as a substrate and propionic acid as the capturing carboxylic acid.[7] They have shown that the addition of an excess of copper bronze (or zinc) as a co-reductant was required for high yields and enantiomeric excesses, in addition to excess **11**. This procedure was also very sensitive to the copper salt with copper(II) acetate proving to be most effective; a structurally well defined bis(aqua)-(*S*)-prolinato-Cu^{II} complex [$Cu^{II}\cdot(H_2O)_2\cdot$(*S*)-proline] was found to behave in an



Scheme 5. The yields and enantiomeric excesses for a variety of synthesized allylic benzoates **3**, **7**, **15–17**.

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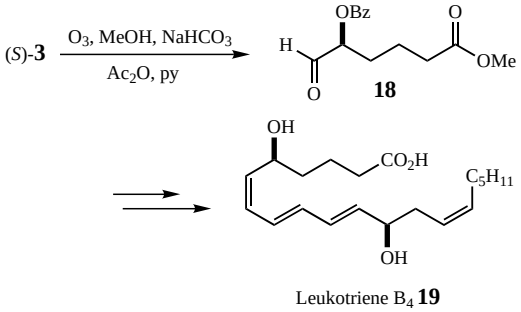
identical manner to the in situ prepared catalyst. (*S*)-Proline (**11**) was similarly found to be the most reliable ligand giving better facial control; any attempt at protecting the nitrogen lone pair only served to lower the enantiomeric excess although when a strained four-membered azetidine-2-carboxylic acid was used, moderate levels of enantioselectivity returned. Feringa has also shown that the yield of cyclohexenyl propionate was affected by the structural nature of the perester oxidant although the enantiomeric excesses were much less influenced. This presumably indicates that the rate of perester decomposition has to fit smoothly and efficiently into the catalytic cycle otherwise the yields are compromised.

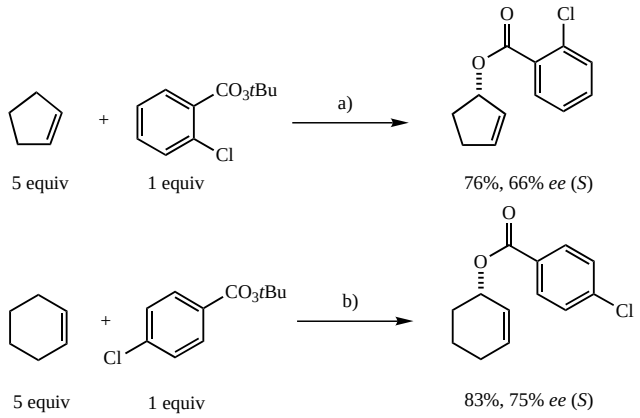
Subsequent studies have developed these initially successful ligand sets. Structural modifications in ligand architectures and peracid oxidant have led to significant improvements, both in terms of yield and enantiomeric excess. Andrus probed the effect of using electron deficient peresters in the presence of the bis(oxazoline) ligands previously reported. Weakening of the perester bond would be expected to lead to more rapid bond homolysis with concomitant increase in the rate of formation of copper(II) benzoate and *tert*-butoxy radical.[8] This strategy was successfully applied to the synthesis of oxoester **18**, a formal intermediate in the synthesis of leukotriene B_4 (Scheme 6). In line with previous reports this methodology was found to be sensitive to the nature of the copper(I) salt, the ligand structure, and the perester employed (Scheme 7). In both cases copper(I) hexafluorophosphate



Scheme 6. A formal synthesis of Leukotriene B_4; py = pyridine.

($CuPF_6$) was found to be the salt of choice, which presumably indicates that a more Lewis acidic copper complex leads to a higher degree of stereocontrol because of more efficient binding of the intermediate allylic radical in the stereochemistry-determining step. The choice of perester and ligand were also found to be important for optimum yield and enantiomeric excess, however, as in previous studies systematic screening of both reagents was required.

Andrus and co-workers have further probed the effect of additional stereogenicity in the bis(oxazoline) backbone by employing the diastereoisomeric biaryl atropisomeric oxazolines **20**, (Scheme 8).[9, 10] The wider bite angle between the two nitrogen atoms and the copper center was expected to improve selectivity for both ligands, by forcing the reacting allyl and benzoate groups

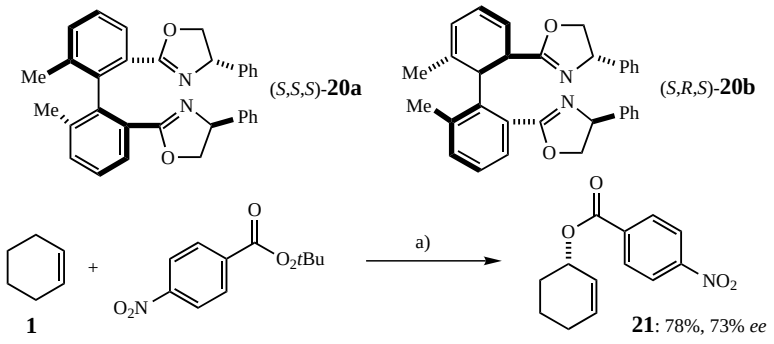


Scheme 7. Allylic oxidation of cyclopentene and cyclohexene using bis(oxazoline) ligands **5**: a) $CuPF_6$ (15 mol%), chiral ligand **5b**, MeCN, −20 °C, 7 days; b) $CuPF_6$ (15 mol%), chiral ligand **5c**, MeCN, −20 °C, 7 days.

closer together in **4**. However, it was found that the (*S*,*S*,*S*)-oxazoline **20a** gave much better stereocontrol than the related (*S*,*R*,*S*) stereoisomer **20b** (76% yield, 0% *ee*). This trend does not appear to be limited to the phenyl substituent within the oxazoline framework of **20**, although the phenyl substituent in **20a** gave better facial control for cyclohexene than either a benzyl or *tert*-butyl substituent. In contrast for cyclopentene the presence of a benzylic group proved to be slightly superior. The absolute stereochemistry in the product allylic ester was remarkably predictable; the (*S*)-configuration being formed exclusively.

Singh and DattaGupta have also extended this methodology by using the tridentate pyridine-based oxazoline **22a** and **22b**.[11] The stereoselectivity was shown to be better using the more substituted oxazoline **22b** for the benchmark cyclohexene oxidation (63% yield, 81% *ee*). The optimized reaction conditions, involving the in situ reduction of copper(II) using hydrazine, followed by the addition of 4 Å molecular sieves, were also effective for cyclopentene (70% yield, 59% *ee*). The more flexible cycloheptene and cyclooctene gave poor levels of asymmetric induction, although the facial control appeared to be independent of the ring size of the starting alkene (Scheme 9).

Kočovský and co-workers have recently found that a bipyridine based ligand **22c** gave better control for larger cycloalkenes (e.g., cycloheptene (62–75% *ee*)) than smaller



Scheme 8. Enantioselective allylic oxidation of **1** using an atropisomeric oxazoline **20**: $CuPF_6$ (10 mol%), chiral ligand **20a** (10 mol%), MeCN, −20 °C, 5 days.

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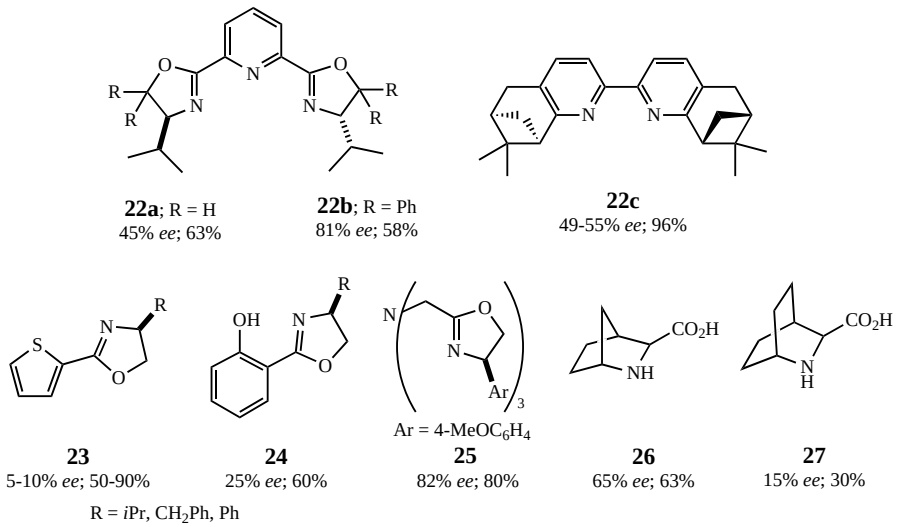


Scheme 9. Yields and enantiomeric excesses for the enantioselective oxidation of cyclohexene.

carbocyclic rings such as cyclopentenes (49 % *ee*) and cyclohexene (49 – 55 % *ee*) (Scheme 9).[12]

Feringa and Zondervan have also investigated the heteroatom topography of a limited series of substituted oxazolines to probe the effect of the nature of the donor atom within the ligand (Scheme 9). Although the softer oxazoline ligand **23**, gave high conversions, the enantioselectivity was low.[13] Slightly higher facial control was observed for the harder phenolic donor **24**, which may indicate that a more strongly coordinated transition state for the copper(III) intermediate **4**, leads to higher stereocontrol, although conversions were only moderate. In the same study the allylic oxidation of cyclohexene by copper(II) (*S*)-proline based complexes was investigated. Moderate enantiocontrol (up to 60 % *ee*) was observed using the naturally available **11** as the chiral ligand. Surprisingly the addition of an additive, anthraquinone, resulted in an increase in the facial selectivity, but only when *tert*-butyl hydroperoxide was used as the oxidant. Using the softer ligand (*S*)-thiaphene **23** caused both the yield and stereoselectivity to be reduced, as did all their other ligand modifications. A negative nonlinear effect was observed for (*S*)-proline itself, that was interestingly reversed to a positive nonlinear effect in the presence of anthraquinone. Although no definitive conclusion as to the nature of the active catalyst was made, it does seem clear from this limited study that a fundamental change in mechanism or structure of the catalyst occurs on addition of the anthaquinone additive.

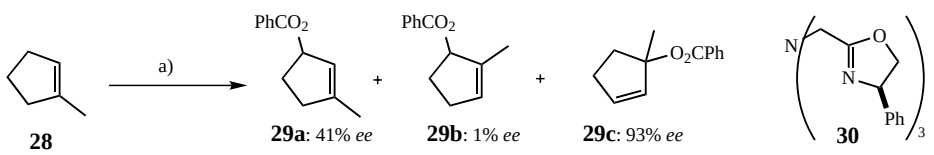
In spite of Ferringa's assertions that modification of the (*S*)-proline skeleton would not result in improved catalyst performance,[13] Andersson and Södergren investigated the effect of introducing a rigid cyclic framework in ligands based on the proline skeleton using a diastereoselective Diels – Alder approach, **26** and **27** (Scheme 9).[14] The bicyclic [2.2.1] ligand **26** gave better stereocontrol than the original (*S*)-proline in the allylic oxidation of cylohexene (63 % yield, 65 % *ee*), however, simple addition of an extra methylene unit in **27** caused a dramatic reduction in the facial control.

Following his initial report,[4] Katsuki has further demonstrated the C_3-symmetric oxazoline **30** (Scheme 10) to be an extremely effective ligand for the stereoselective oxidation of cyclopentene. During this study it was discovered that the enantiomeric excess of the product, such as benzoate **3**, decreased as the reaction time became longer.[15] The simple addition of 4 Å molecular sieves to the acetone reaction mixture suppressed this racemization leading to 83 % yield and 76 % *ee*. Reduction in temperature was further shown to increase the enantioselectivity (up to 93 % *ee*) although the yields dropped dramatically. These optimized conditions were also shown to be effective for other cyclic alkenes, although the selectivity and turnovers were inferior. Although, recently, the selectivity has been improved using the related oxazoline **25** (Scheme 9).

The regioselective oxidation of 1-methylpentene (**28**), in keeping with the earlier findings of Pfaltz and co-workers,[2] produced three positional isomeric allylic benzoates **29a – c**, with dramatically different enantiomeric excess (Scheme 10). The enantioselectivity was evidently dependent on the structural nature of the intermediate allylic radical. No oxidation of the allylic methyl C–H unit was observed.

Katsuki and Kohmura have also elegantly shown that this procedure can be extended towards the deracemization of racemic substituted cyclopentenes **31** to give the enantiomerically enriched allylic benzoates **33** (81 % *ee*), **34** (58 % *ee*), and **35** (85 % *ee*) in an overall 38 % yield (Scheme 11).[16, 17] The reaction must proceed via an interconverting pair of enantiomeric allylic radicals **32a** and **32b**. The C_3-symmetric tris(oxazoline) **30** gave the best facial control, whereas, the more common C_2-symmetric based oxazoline ligand **5** gave lower levels of control.

Currently, there are a only limited number of applications of this methodology, primarily because of the infancy of this asymmetric reaction.[8] In view of the potential utility and versatility of this transformation within organic synthesis, it seems likely that further applications will soon appear. Before this can occur, a generic catalytic system is clearly required. Presumably this will follow on from better mechanistic



29a:**29b**:**29c** = 67:25:3

Scheme 10. Regioselective oxidation of **28**: a) $Cu(OTf)_2$ – **30** (5 mol %), $PhCO_3tBu$, acetone, 0 °C.

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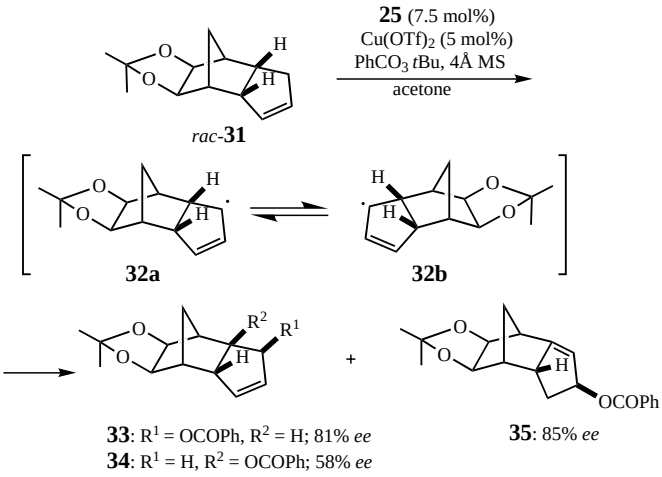

Scheme 11. The deracemization of alkene *rac*-**31** using an allylic oxidation strategy. Ratio **33**:**34**:**35** = 57:24:19; yield 38%; MS = molecular sieves.

understanding of the complex reaction and the role of particular additives. In addition, some general problems need addressing, such as the requirement for high alkene concentrations, the long reaction times and apparent substrate restrictions before the potential of this reaction can be truly realized.

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