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Synthesis of All-Carbon, Quaternary Center-Containing Cyclohexenones through an Organocatalyzed, Multicomponent Coupling

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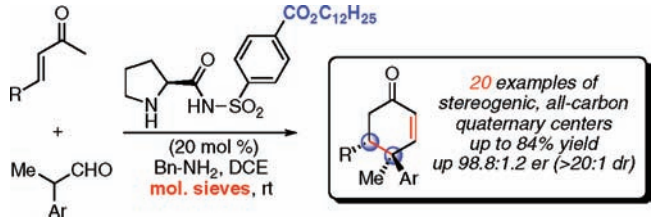
ABSTRACT



Organocatalyzed multicomponent coupling using a new ester-containing, proline aryl sulfonamide has been developed for accessing densely functionalized cyclohexenones, each containing a quaternary center in high enantio- and diastereoselectivity. In contrast to most enamine/iminium-catalyzed reactions, the use of molecular sieves was critical to optimum enantioselectivity.

In the history of enantioselective organic synthesis, the Hajos−Parrish−Eder−Sauer−Wiechert reaction[1] represents one of the first (and still most powerful) transformations developed for accessing stereogenic (all-carbon) quaternary centers[2] (Scheme 1, eq 1). The widespread presence of this functionality in natural products has made their construction a central focus of organic chemistry.[3] The Hajos−Parrish reaction generally necessitates that the quaternary center be first established on an achiral substrate.[4] The prochiral position is then rendered enantiomerically enriched through an intramolecular aldol desymmetrization event, normally catalyzed by the amino acid proline. Recent examples from several laboratories have utilized the Michael addition itself as the enantiodetermining step via transition-metal,[5] Brønsted acid,[6] and phase-transfer catalysis.[7] The vast majority of these cases have employed two resonance electron-withdrawing groups on the nucleophilic component, with carbon-based electron-withdrawing groups normally limited to ketones, esters, and nitriles.

In contrast, attempts to exploit aldehyde moieties within the nucleophilic component (e.g., **5**) of a Hajos−Parrish-type reaction have met with only limited success to date (Scheme 1, eq 2), despite the fact that racemic methods have

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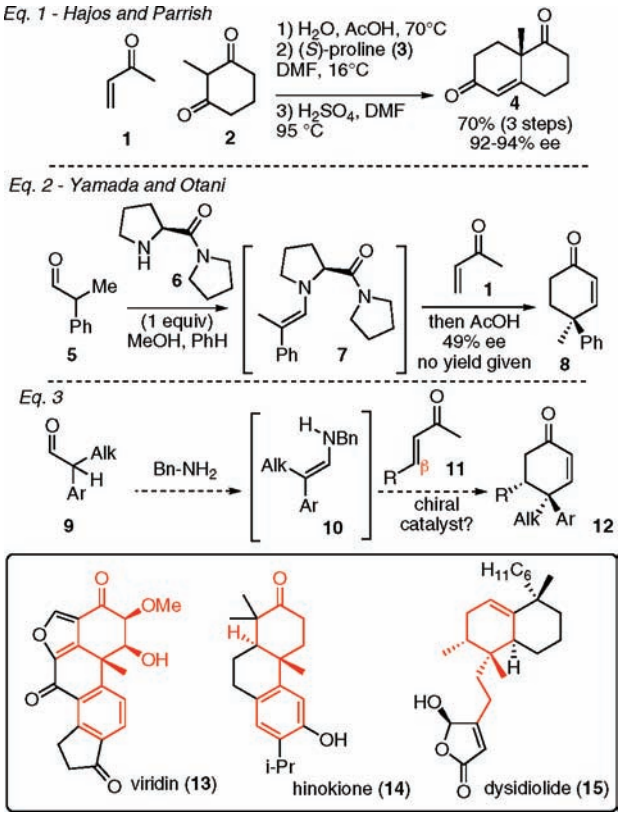
Scheme 1. Enantioselective Robinson Annulations



been known for some time.[8] In 1969, Yamada and Otani reported a protocol that employed stoichiometric proline derivative **6** to facilitate the one-pot Robinson annulation of 2-phenylpropanal (**5**) and methyl vinyl ketone (**1**) in modest enantioselectivity (up to 49% ee).[9] Despite this encouraging early report, the concept has laid essentially dormant over the next four decades,[10] likely due to the inability to turn over the catalyst and the disappointing levels of enantioselectivity.[11] One major limitation of this chemistry to date is the lack of substitution on the β-position of the enone moiety (e.g., compound **11**).[9−12] Bella[13] and our laboratory[14] have separately reported examples of successful Michael additions of α,α-disubstituted aldehydes to cyclohexenone; however, the products from these reactions are inherently incapable of undergoing elimination. Acyclic enone substrates bring the added challenge of controlling rotational freedom around the σ bond connecting the alkene and ketone moieties.[15] This rotational freedom is not a stereochemical issue with unsubstituted acyclic enones such as methyl vinyl ketone. If a one-step method could be developed to provide useful levels of enantio- and diastereoselectivity on acyclic, β-substituted enones (e.g., Scheme 1, eq 3), the annulation product **12** might prove to be a powerful synthetic building block as illustrated by its presence in natural products such as viridin (**13**)[16] and hinokione (**14**)[17] as well as manipulation of the benzene ring to provide access to other natural product scaffolds such as dysidolide (**15**).[18]

One option to facilitate catalyst turnover would be the addition of an achiral additive, which might also help to augment the nucleophilicity of the aldehyde component **9**. Recently, our laboratory demonstrated that benzylamine is effective in this role through presumably the transient formation of enamine **10** and its subsequent reaction with cyclohexenone to make bicyclo[2.2.2]octanone scaffolds.[14b] Herein, we disclose the synthesis of enantioenriched enones **12** containing two contiguous stereogenic centers including an all-carbon-quaternary carbon through an organocatalyzed, multicomponent coupling.

Our exploration of this transformation is shown in Table 1. We selected 3(*E*)-penten-2-one (**18**) as our initial Michael acceptor for the tranformation. We were pleased to observe that enone **20** could be formed by using benzylamine as an additive in the presence of catalyst **17** (Table 1, entry a). Our laboratory has developed a proline aryl sulfonamide derivative (2*S*)-*N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide (**17**) containing a lipophilic side arm, which imparts significantly improved solubility in nonpolar solvent systems.[19] Under these conditions, it appears the initial Mannich addition product (e.g., **19**) undergoes rapid elimination to generate the corresponding enone **20**. Benzylamine is critical to the success of this reaction as no product is observed in its absence. While benzylamine is potentially catalytic in this reaction, use of less than 1 equiv led to

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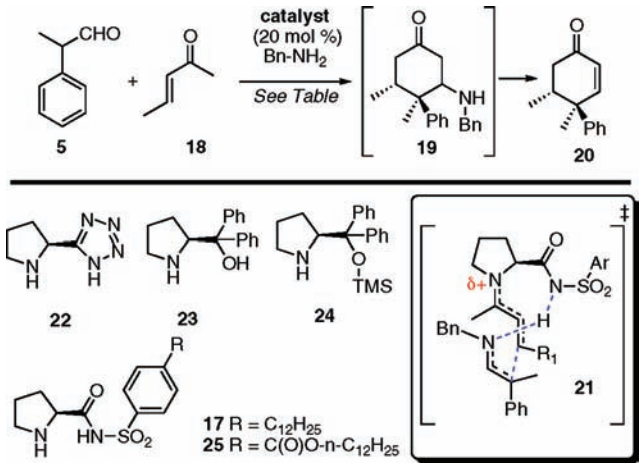
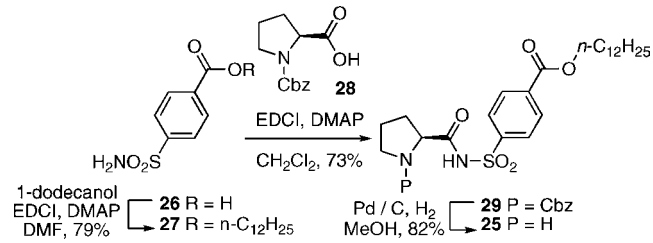
Table 1. Optimization of Multicomponent Coupling Reaction



entry	conditions	catalyst	yield (%)	er (dr)
a	PhMe, 24 h, rt	**17**	30	77.3:22.7 (>20:1)
b	PhMe, 36 h, rt, mol. sieves	**17**	66	90.7:9.3 (>20:1)
c	4-F-$C_6H_4CO_2H$ (20 mol %), PhMe, 20 h, rt, mol sieves	**17**	60	76.7:23.3 (>20:1)
d	PhMe, 60 h, rt, mol sieves	**3**	32	84.4:15.6 (>20:1)
e	PhMe, 60 h, rt, mol sieves	**22**	11	62:38 (20:1)
f	PhMe, 60 h, rt, mol sieves	**23**	trace	
g	PhMe, 60 h, rt, mol sieves	**24**	trace	
h	DCE, 60 h, rt, mol sieves	**17**	67	92.1:7.9 (>20:1)
i	*DCE, 60 h, rt, mol sieves*	***25***	*75*	*94.6:5.4 (>20:1)*
j	DCE, 48 h, rt	**25**	66	85.7:14.3 (>20:1)
k	CH_2Cl_2, 60 h, rt, mol sieves	**25**	77	93.4:6.6 (20:1)

appreciably slower rates.[20] The presence of molecular sieves in the reaction mixture had a beneficial effect on the reaction profile, leading to increased chemical yield and enantioselectivity (Table 1, entry b). This result is counter to what is often observed in organocatalyzed processes where water can have a beneficial impact on the reaction.[14,19,21] We are unsure as to the exact nature of the difference, but one possibility may be that water disrupts a presumed hydrogen-bonding interaction between the catalyst and enamine nucleophile as shown in tentative and empirically derived model **21**. A more detailed mechanistic discussion can be found in our previous publications.[14] Melchiorre and co-workers have successfully utilized fluorobenzoic acid additives with organocatalysts in a range of chemical transformations.[22] Unfortunately, addition of 4-fluorobenzoic acid (20 mol %) led to a significant decrease in enantioselectivity (Table 1, entry c). Use of several other standard organocatalysts also proved ineffective for transformation (Table 1, entries d−g). Both proline (**3**) and tetrazole **22**[23] gave reduced chemical yields and lower enantioselectivities (Table 1, entries d and e). The prolinol catalyst **23** and its silyl derivative **24** were ineffective at generating the desired product (Table 1, entries f and g). Previously, we have shown that chlorinated solvents can be advantageous to reaction selectivity (Table 1, entry h).[19] Interestingly, use of a modified form of the parent aryl sulfonamide catalyst, namely the *p*-dodecylester **25**, proved more effective at accomplishing this transformation (Table 1, entry i). This catalyst can be readily prepared from inexpensive starting materials (Scheme 2). The presence of molecular sieves continued to be critical to the enantioselectivity of this transformation (Table 1, entry j). It should be noted that the sequestering of water by molecular sieves complicates any mechanism for catalyst turnover, which may in part explain the observed rate of reaction. Attempts to accelerate the rate of this transformation using additive ethyl 3,4-dihydroxybenzoate[12] proved deleterious to the enantioselectivity of the reaction. The optimized, one-step protocol (Table 1, entry i) constitutes the first enantioselective synthesis of compound **20**, a natural product that has been isolated from pine needles by Zhou and co-workers.[24] Prior efforts to access this general scaffold have focused on metal-catalyzed conjugate addition to desymmetrize an achiral cyclohexadienone structures[25] or palladium-mediated couplings of β,γ-unsaturated cyclic ketones.[26]

Scheme 2. Synthesis of Sulfonamide Catalyst **25**



Initial exploration of the reaction scope for the acyclic enones is shown in Table 2. A variety of aldehyde compo-

(20) The use of (*R*)- or (*S*)-α-methylbenzylamine was ineffective in the transformation, leading to no observed product. See: Pfau, M.; Revial, G.; J. d'Angelo, A. G. *J. Am. Chem. Soc.* **1985**, *107*, 273–274.

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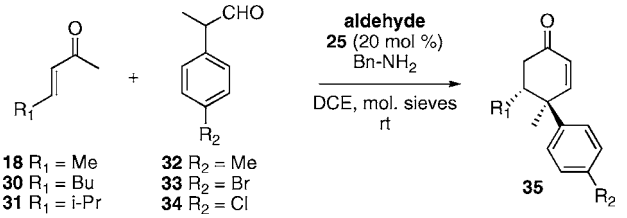
Table 2. Initial Exploration of Reaction Scope



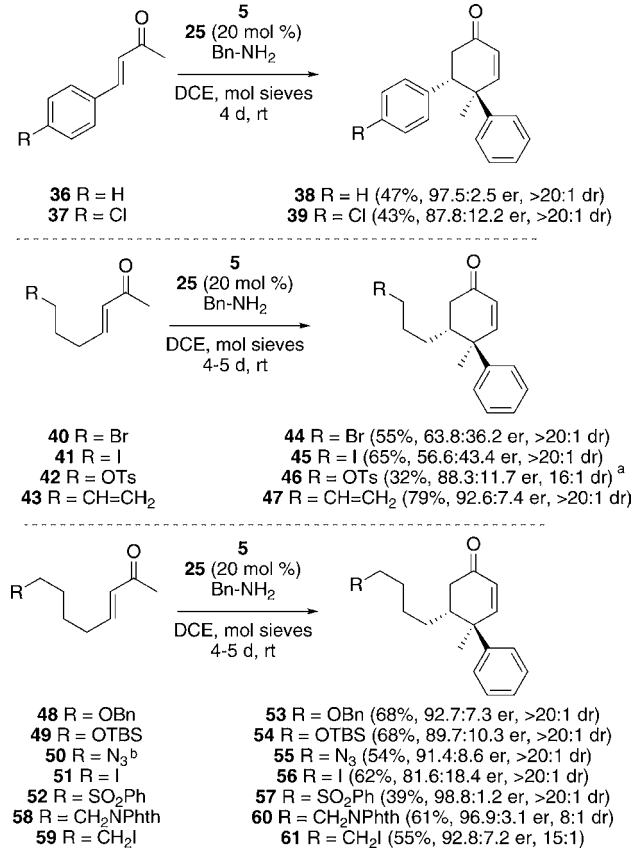
entry	enone	aldehyde	time (h)	yield (%)	er (dr)
a	**18**	**32**	60	56	94.4:5.6 (>20:1) R_1 = Me, R_2 = Me
b	**18**	**33**	60	54	93.6:6.4 (>20:1) R_1 = Me, R_2 = Br
c	**18**	**34**	60	52	93.6:6.4 (>20:1) R_1 = Me, R_2 = Cl
d	**30**	**5**	72	84	95.7:4.3 (>20:1) R_1 = Bu, R_2 = H
e	**30**	**32**	72	76	91.5:8.5 (>20:1) R_1 = Bu, R_2 = Me
f	**30**	**33**	72	68	95.9:4.1 (>20:1) R_1 = Br, R_2 = Br
g	**31**	**5**	60	0	R_1 = i-Pr, R_2 = H

nents can be utilized in this transformation. X-ray crystallographic analysis of product **35b** allowed for the establishment of absolute configuration. Interestingly, 3-octen-2-one appears to be generally more effective than 3-penten-2-one in the transformation. This result may in part be due to the comparable purity of the commercial **30**. One limitation was isopropyl-substituted enone **31**, which was unreactive under the reaction conditions (Table 1, entry g).

A range of alternate subsituents on the β-position of the enone were also explored (Scheme 3). Aromatic moieties appeared to be tolerated, providing the desired products **38** and **39** in good to excellent enantioselectivity. A variety of aliphatic subsituents can be accommodated as shown with enones **40**−**43**, **48**−**52**, and **58**−**59**. In the majority of cases, good chemical yields and high stereoselectivities were observed. One limitation appears to be the use of propyl halides subsituents on the enone, compounds **44** and **45**; however, use of the corresponding tosylate **42** led to improved levels of enantioselectivity. Alkenes, sulfones, silyl and benzyl ethers, as well as phthamide nitrogens were all tolerated under the reaction conditions. Interestingly, the annulation reaction to form cyclohexenone **55** was performed in the dark to suppress an unwanted intramolecular [3 + 2] cycloaddition, which consumed enone **50**.

In summary, a rapid, multicomponent coupling method has been developed for accessing two contiguous stereogenic centers on a cyclohexenone scaffold including an all-carbon quaternary center in a highly enantio- and diastereoselective fashion (up to 98.8:1.2 er and >20:1 dr) in generally good chemical yield (average chemical yield for the 20 products

Scheme 3. Further Exploration of Reaction Scope



[a] This reaction was run using catalyst **17**. Use of catalyst **25** gave lower levels of enantioselectivity (80:20 er). [b] This reaction was performed in the absence of light.

produced: 60%). A range of substituents is tolerated on both the aldehyde and enone components. A novel sulfonamide catalyst **25** has also been developed for use in these organocatalyzed processes. Further applications of this technology will be reported in due course.

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Supporting Information Available: Complete experimental procedures are provided, including ^{1}H and ^{13}C spectra, of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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