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Squaramide-Catalyzed Enantioselective Michael Addition of MaskedAcyl Cyanides to Substituted Enones

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ABSTRACT: Masked acyl cyanide (MAC) reagents are shown to be effective ump lung synthase for enantiose-lective Michael addition to substituted emotes. Their actions are catalyzed by chiral squaramides and afford adducts in high yields (90−99%) and with excellent nation selectivity's (85−98%). The addition products areunmasked to produce cyanohydrins that, upon treatment with a variety of nucleophiles, provideγ-keto acids, esters,and amides. The use of this ump lung symphony hasenabled, in enantiomerically enriched form, thefirst total synthesis of the prenylated phenol (+)-fornicin C.

The importance of umpolung chemistry stems from itscapacity to provide access to functional group arrange-ments that are difficult to realize through normal chemicalreactivity considerations.1For example, whereas 1,3-dicarbonylcompounds are readily synthesized through classical reactivity(nucleophilic enolate plus an electrophilic carbonyl reactant),1,4-dicarbonyl compounds, having dissonant connectivity,2canprove challenging. An efficient route to such compounds isthrough an umpolung strategy, the reaction of an ionone with am asked acyl anion. Given their value in synthesis, many acylation equivalents have been developed and utilized for a variety of synthesis problems.3Among useful and versatile umpolung synthase are protected hydroxyl malononitriles, known as masked acyl cyanide (MAC) reagents, developed by Yamamotoand Nemoto.4Treatment of a MAC reagent with base generates nucleophile acyl anion equivalent that will react with a variety of electrophilic units.

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Subsequent unmasking of the MAC unit produces an acyl cyanide, which can be intercepted to affordcarboxylic acids, esters, or amides.5Thus, unlike typical acylanion equivalents, MAC reagents also harbor masked acidchloride-like reactivity. This dual capability, found in few acylanion equivalents, allows MAC reagents to function as carbonmonoxide equivalents.6The usefulness of these reagents isdemonstrated by their use in the total syntheses of (−)-bestatin,cyclotheonamide C, and oseltamivir (tamiflu).7−9Despite theirimportance in synthesis, there appears to be no report of acatalytic enantioselective reaction of a MAC reagent.10The easeof deprotonation of MAC reagents suggested that their reactionscould be rendered enantioselective using a bifunctional chiralbase. In this report, we disclose thefirst enantioselectivereactions of the MAC family of umpolung synthons.11,12Specifically, we show that Michael additions of MAC reagentsto enones are efficiently catalyzed by chiral squaramides,affording adducts in high yields and excellent enantioselectivitie

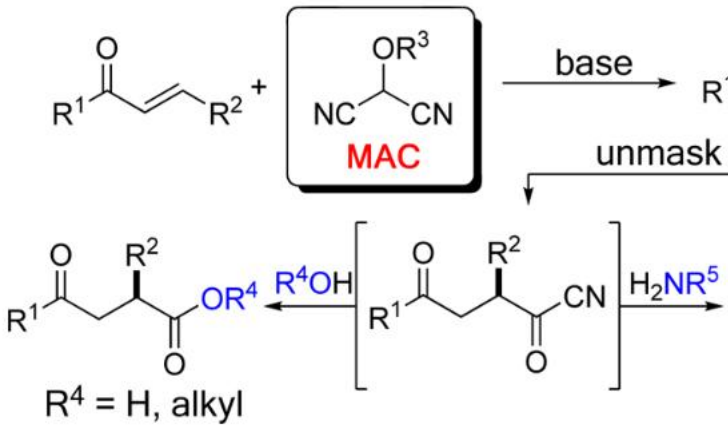

Figure 1.Synthesis of 1,4-dicarbonyls via addition of MAC reagents.

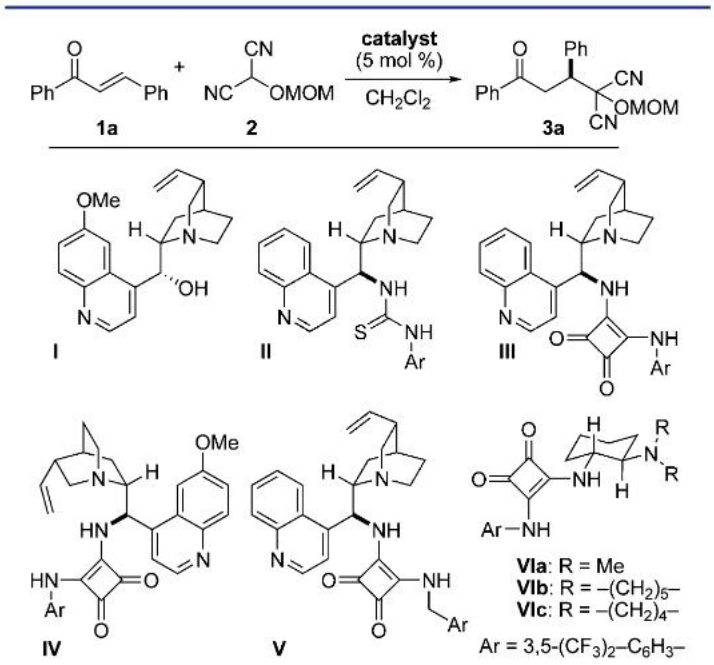

Figure 2.A selection of chiral catalysts examined.

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nd, upon unmasking, provide ready access to chiralγ-keto-carboxylic acids, -esters, and -amides (Figure 1).Our initial efforts focused on the identification of effectivecatalysts and conditions for the enantioselective Michael reactionbetweentrans-chalcone (1a) and MOM-MAC (2)toaffordadduct3a(Figure 2).13,14Although quinine (I) promoted thisreaction, it afforded the adduct with poor enantioselectivity. Thecinchonidine-derived thiourea catalyst (II) gave better enantio-selectivity but low conversion. On the other hand, thecorresponding squaramide (III)provided both superiorconversion and enantioselectivity. As anticipated, the pseudo enantiomeric, quinidine-derived squaramide (IV)provided theproduct with comparable selectivity and conversion but enrichedin the opposite enantiomer. Among the other squaramidecatalysts examined, those based on 1,2-diaminocyclohexaneproved most effective, particularly the pyrrolidine catalystVIc,which formed3aat a high rate and with 90% ee.15,16Theenantiomeric excess improved significantly, to 97%, when thereaction was carried out at−30°C. It is noteworthy thatcomparable enantioselectivity was observed even at 1 mol %catalyst loading, albeit withlower conversion. Moreover,increasing the catalyst loading to 10 mol % did not significantlyincrease the conversion over the 5 mol % reaction, presumablydue to the limited solubility of the catalyst.17Additional solventswere also investigated for the reaction, but they did not lead to animproved outcome.We next examined the practical utility and substrate scope ofsquaramide-catalyzed enantioselective Michael reactions ofMAC reagents (Table 1). In general, high yields andenantioselectivities were observed for a broad range of enones.Importantly, the related TBS-MAC reagent (4)4bwas also foundto be effective for the enantioselective Michael reaction.Although4displays lower reactivity compared to2, requiringhigher reaction temperatures and/or longer times for completereaction, it provides comparable enantioselectivity while offeringan alternative deprotection protocol (vide infra). Enones having.

electron-deficient aryl groups at theβ-position gave excellentresults (entries 2−3). The more electron-rich substrate,p-methoxyphenyl enone1d, required higher

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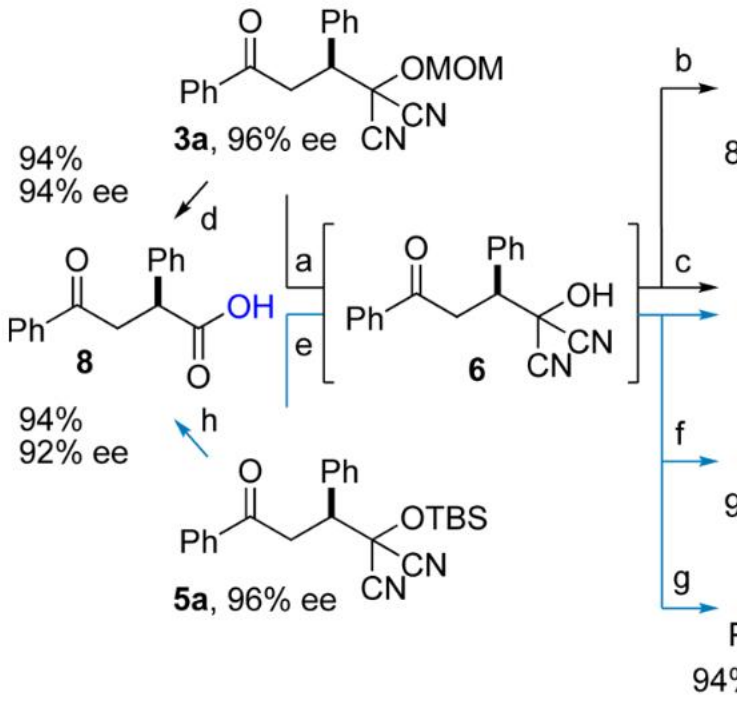
reaction temperaturesand provided reduced enantioselection (entry 4). The Michaeladdition was also effective with naphthyl enone1eand variousheteroaryl-substituted enones (entries 5−9). Conjugated enone1jreacted selectively at theβ-position to afford the additionproducts in excellent yields and enantioselectivities (entry 10).The related substituted dienone1kdelivered the additionproduct with a notable drop in enantioselectivity, coinciding withits reduced reactivity (entry 11). The reaction of enone1l, whichcontains a free phenol, is noteworthy as it demonstrates thetolerance for acidic hydrogen-bond donor groups in the substrate(entry 12). The successful use of benzotriazole-containing enone1m(entry 13) is noteworthy.Enones havingβ-alkyl-substituents were also found to beeffective substrates for the MAC-Michael reaction.18Thereaction of both MAC reagents with enones having primaryalkyl substitutents proceeded well, affording the additionproducts in near-quantitative yields and with high enantiose-lectivities (entries 14−16). The more sterically hinderedcyclohexyl-enone1q(entry 17) required room temperature forthe reaction to proceed but still gave the product with 89% ee.Cyclopropyl enone1r, on the other hand, was more reactive andgave the addition product in excellent yield and selectivity (entry)



18). The Michael reaction of MOM-MAC and trifluoromethyl-substituted enone1sproceeded nicely, providing straightforwardaccess to chiral units containing the trifluoromethyl group.Curiously, for reasons that are unclear, the same reaction withTBS-MAC gave significantly lower selectivity with this substrate.The optimized conditions are

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suitable for the preparation ofgram quantities of the Michael adducts. For example, the reactionwith chalcone1awas scaled up to produce 1 g of product, formedin the same yield and enantioselectivity as noted in entry 1.Additionally, in large-scale reactions the low solubility of thecatalyst makes it convenient to recover most of it (84%) from theether extracts by simplefiltration. Such recovered catalyst can beused multiple times without measurable loss in efficacy.We recognized that the above reactions would be of value onlyif the MAC group in the Michael adducts could be transformedinto useful functional groups without eroding enantioselectivity.A careful examination of hydrolysis conditions allowed us toidentify mild, efficacious conditions for unmasking the MACmoiety. For the MOM-MAC adduct3a, excellent results wereobtained if the intermediate acyl cyanide, which is prone toracemization, was intercepted at a relatively low temperature (ca.−40°C).19Thus, treatment of the labile dicyanohydrin (6),formed upon removal of the MOM group, at−40°C withMeOH/Et3N or morpholine/Et3N, gave ketoester7orketoamide9, respectively, in high yields and with little or noenantiomeric excess loss (Scheme 1). Ketoacid (8) can beformed directly by treating the MOM-adduct with CSA inaqueous acetic acid. Conditions were also developed for theefficient transformation of the TBS-MAC adduct5ato methylester7, Weinreb amide10, and glycine-derived amide11as wellas for its direct transformation to ketoacid8.20The absolute stereochemistry induced during the Michaelreaction was determined by taking advantage of the uniquereactivity of acyl benzotriazoles.21The MAC addition product ofcinnamyl-benzotriazole (1m) catalyzed by (R,R)-VIcwasfirstconverted to methyl ester12, unmasking of which generated theknown succinate ester13, enriched in theSenantiomer (Scheme2). The observed asymmetric induction is consistent with apretransition state assembly shown in Figure 3, wherein theammonium salt directs nucleophilic addition of MAC anion to

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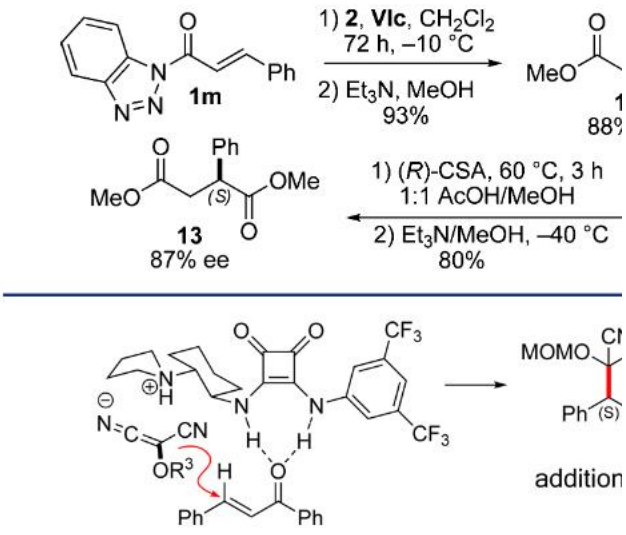
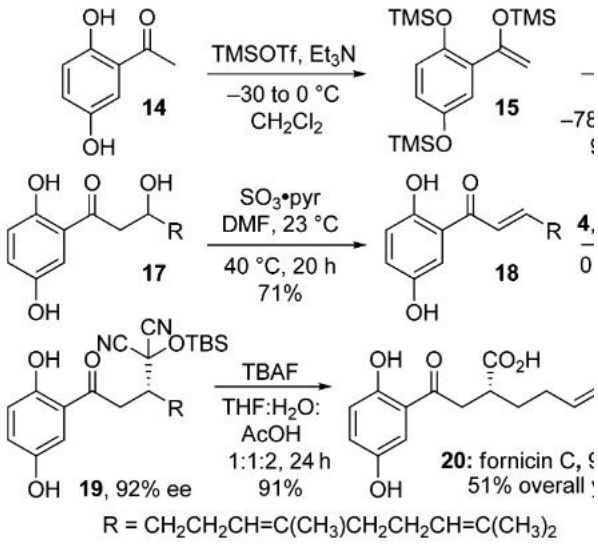


Figure 3.Model for asymmetric induction



chalcone, which in turn is activated through hydrogen bonding.Analogous models have been posited for thiourea- andsquaramide-catalyzed asymmetric reactions.14b,hThe utility of the above enantioselective methodology isdemonstrated through the total synthesis of prenylated phenol(+)-fornicin C (Scheme 3). Isolated fromGanoderma fornicatum,extracts of which are reported in Chinese medicine to havehealth-promoting properties,22fornicin C displays moderate invitro cytotoxic activity against the human larynx carcinoma cellline Hep-2 (23μg/mL). Triol17can be prepared directly fromthe aldol reaction of the trianion of 2,5-dihydroxyacetophenone(14) with geraniol-derived aldehyde16in ca. 50% yield23or in ahigher yield via the Mukaiyama aldol reaction of silyl enol ether15with16. Dehydration to the enone was an unforeseenchallenge since basic conditions promoted cyclization to achromanone, while strongly acidic conditions introducedcomplications through reactions with the geranyl side chain.Furthermore, with dehydrating agents such as Martin's sulfuraneor Burgess'reagent, the phenols competed with the secondaryalcohol. We found that sulfur trioxide-pyridine complex waseffective in achieving the dehydration of triol17to enone18.24Addition of TBS-MAC (4) to enone18provided adduct19with92% ee.25When subjected to AcOH-buffered

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TBAF,19wassuccessfully unmasked to reveal (+)-fornicin C in 51% overallyield, with complete retention of ee.To summarize, we have developed thefirst catalytic,enantioselective reaction of the MAC family of umpolungsynthons. We have shown that chiral squaramideVIccatalyzes the conjugate addition reactions of MAC reagents2and4to acollection of electronically and structurally diverse enones toafford adducts in high yields and with excellent enantioselectiv-ities. The addition products can be unmasked to affordγ-keto-carboxylic acids, -esters, and -amides, all formed in excellentyields and with near complete retention of enantiomericexcesses. We have utilized this methodology for the totalsynthesis of (+)-fornicin C, prepared infive steps from knownaldehyde16, in 51% overall yield and 92% ee. The developmentof other enantioselective reactions of MAC and relatedumpolung reagents is expected to be of great value in organicsynthesis.

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