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Squaramide Organocatalyzed Addition of a Masked Acyl Cyanide to β-Nitrostyrenes

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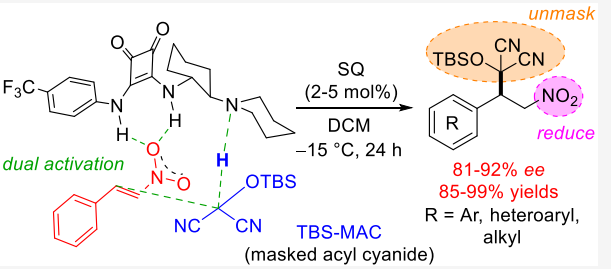
ABSTRACT: A method for the squaramide-organocatalyzed enantioselective addition of a silyl-protected masked acyl cyanide (MAC) reagent to various β-nitrostyrenes is described. Reactions are carried out in a freezer and provide products cleanly and in high enantioselectivities at very low catalyst loadings. Adducts are then unmasked, providing various oxidation state 3 functional groups, thereby highlighting the utility of these MAC reagents and a new strategy for the preparation of β-amino acids.



Nontraditional umpolung reactivity has allowed seemingly impossible bond forming reactions to be realized.[1] An acyl anion equivalent is an umpolung synthon of the acyl carbon, reversing the electrophilic site to be employed as the nucleophile. The acyl anion synthon is deprotonated to generate the nucleophilic oxidation state 2 species. Examples include cyanide, dithiane,[2] hydrazone,[3] metalated enol, and nitronate.[4,5] The power of the synthon is further realized when it serves as a traceless linchpin, bringing together two components. These equivalents contain an increased oxidation state such as silyl dithiane,[6] trichloromethylcarbinol,[7] and masked acyl cyanides (MAC)[8] (Figure 1).

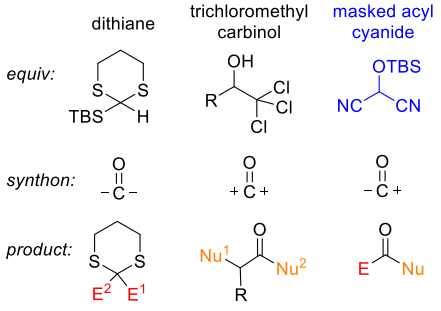
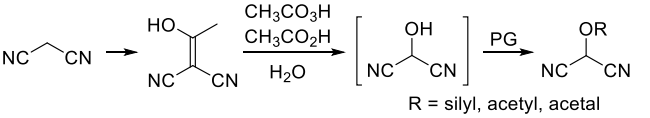


Figure 1. Representative acyl anion equivalents.

The synthesis of MAC reagents involves an intermediate hydroxymalononitrile, allowing derivatization to various protecting groups as in Scheme 1 (R = silyl (TBS, TIPS, TBDPS), ester (Ac and other derivatives), and acetal (MOM, EE)).[9−12] Unlike traditional umpolung reagents, the increased acidity of the methine hydrogen does not require strong alkyllithium bases to generate the acyl anion equivalent.[9b] Weak tertiary amine bases or bicarbonates are sufficient to achieve deprotonation, allowing both TBS-MAC and MOM-MAC, and to a lesser extent Ac-MAC, to be exploited in a variety of bond transformations including alkylations,[8,13,14] addition to imines[8,15,16] and aldehydes,[11,17−20] as well as conjugate addition to enones[10,21] and quinone methides.[22] MAC has also been used as a one carbon homologue in the total synthesis of complex natural products.[23−28] Only recently has the enantioselective addition of MAC reagents been realized through the organocatalyzed addition to imines[16] and enones[10] and an iridium-catalyzed allylic alkylation.[14]

Scheme 1. Synthesis of MAC Reagents



Our group utilizes MAC reagents to access chiral building blocks and in the design of small molecule inhibitors of the HIV integrase enzyme.[20] Our interest in various projects necessitated gram scale preparation of the silyl-protected MAC reagent, TBS-MAC, which we have recently developed in a scalable and detailed preparation.[12] Given the importance of chiral β-amino acids,[29] we envisioned an organocatalyzed addition of MAC to substituted phenyl β-nitrostyrenes to access the precursor α-aryl-β-nitropropanoic esters (Scheme 2c, after unmasking). In 2015, Zhang reported an enantioselective iridium-catalyzed hydrogenation of α-aryl-β-nitroacrylates to yield α-aryl-β-nitropropanoic esters (Scheme

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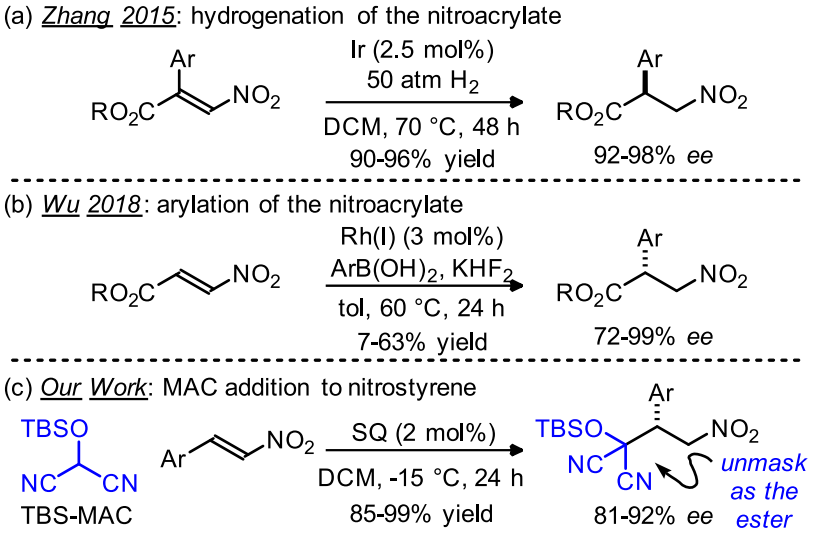
Scheme 2. Approaches to Chiral β^2-Amino Acid Precursors



2a).[30] In 2018, Wu described the rhodium-catalyzed addition of aryl boronic acids to nitroacrylate (Scheme 2b).[31] Our approach is complementary, both in design of the substrate and the catalyst type, to provide valuable chiral building blocks as precursors to chiral β^2-amino acids.

We identified both squaramide (SQ) and thiourea (TU) catalysts as ideal for the conjugate addition as they can activate both β-nitrostyrene and TBS-MAC via noncovalent interactions. Accordingly, we screened commercially available SQ I–III (entries 1–6) and TU IV–V (entries 7–11) with unsubstituted phenyl β-nitrostyrene **1a** with TBS-MAC **2** in DCM at 0 °C (Table 1). Reactions were monitored by TLC at 1, 4, 8, and 24 h. These initial results were quite promising with full conversion to **3a** observed within 24 h at very low catalyst loadings of only 0.5 mol % for all but TU IVd, which contains a bulky isoindoline ring (entry 10). The *ee*'s were ≥50% for all the SQ catalysts (entries 1–6) and 2 of the TU catalysts (entries 7 and 8). Three of the highest selectivities observed were with catalysts containing the piperidine ring (79% *ee* for SQ IIIa (entry 3), 81% *ee* for SQ IIId (entry 6), and 66% *ee* for TU IVa, entry 7). We chose SQ IIId and undertook a solvent screen to maximize *ee*.

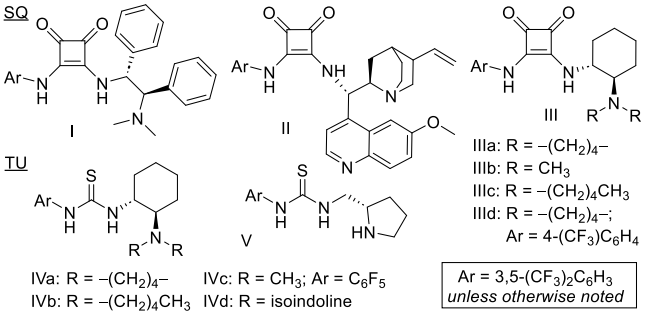
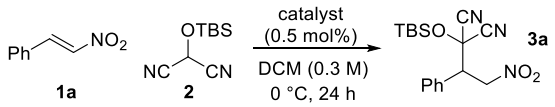


Table 2 summarizes the results of a solvent screen conducted at 0 °C (full screen in the Supporting Information). A wide range of solvents were well tolerated and resulted in the formation of product (**3a**) at the same low catalyst loading as

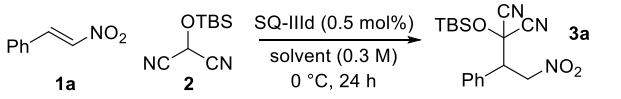
Table 1. Screen of Organocatalysts[a]



entry	catalyst	time (h)	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	I	24	100	65	50
2	II	8	100	84	72
3	IIIa	24	100	74	79
4	IIIb	24	100	79	51
5	IIIc	24	100	80	75
6	IIId	24	100	76	81
7	IVa	8	100	83	66
8	IVb	8	100	78	70
9	IVc	5	98	92	28
10	IVd	24	77	60	17
11	V	24	98	76	12

[a]Reaction conditions: catalyst (0.5 mol %) was added to **1a** (0.2 mmol) and **2** (1.1 equiv) in DCM (0.3 M) at 0 °C and stirred 24 h. Reactions were filtered through a small SiO_2 plug and rinsed with DCM (3 × 1 mL) to remove the catalyst. [b]Reactions were monitored by TLC at 1, 4, 8, and 24 h. Once complete by TLC, they were checked by ^{1}H NMR for conversion in relation to starting **1a**. [c]Yield refers to isolated pure **3a**. [d]The *ee* of **3a** was determined by chiral HPLC.

Table 2. Solvent Screen with Squaramide IIId[a]



entry	solvent	yield[b] (%)	ee[c] (%)
1	hexanes	67	77
2	toluene	79	77
3	$C_6H_5CF_3$	86	82
4	CH_2Cl_2	76	81
5	$CHCl_3$	74	86
6	CCl_4	76	78
7	Et_2O	85	61

[a]General conditions: SQ-IIId (0.5 mol %) was added to **1a** (0.2 mmol) and **2** (1.1 equiv) in solvent (0.3 M) at 0 °C and stirred for 24 h. Reactions were filtered through a small SiO_2 plug and rinsed with DCM (3 × 1 mL) to remove the catalyst. [b]Yield refers to isolated pure **3a**. [c]The *ee* of **3a** was determined by chiral HPLC.

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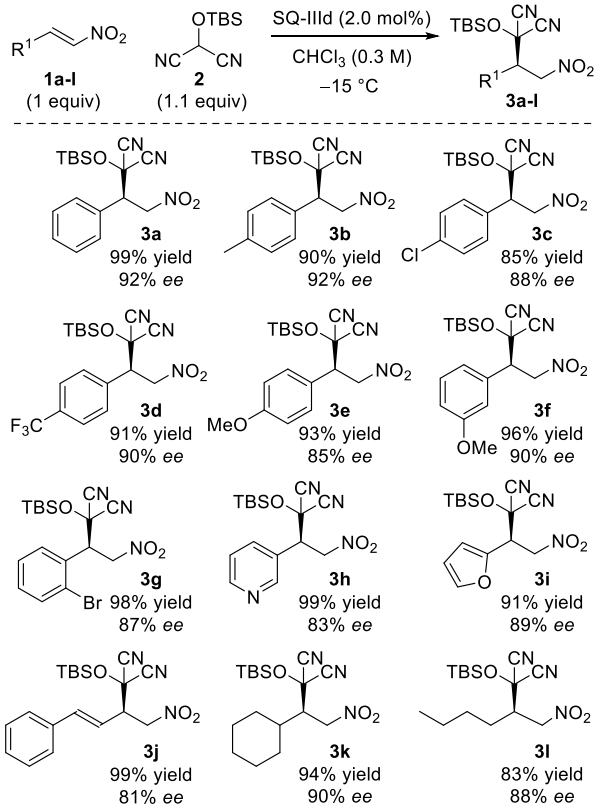
in Table 1. The best solvents were those that are nonpolar (entries 1−6). Halogenated solvents showed slight improvement over their hydrocarbon equivalents (entry 3 vs entry 2; entries 4−6 vs entry 1). Solvents containing a heteroatom such as oxygen, nitrogen, or a free OH provided moderate conversions but low selectivities, presumably due to disruption of noncovalent interactions (entry 7). Overall, chloroform provided the best yield and enantioselectivity (entry 5, 74% yield, 86% *ee*).

We then studied the temperature and order of the addition of reagents to increase *ee*. The solvent screen was run with reactions in the refrigerator (0 to 2 °C). We found that moving the reaction to the freezer (−15 to −18 °C) provided a slightly higher enantioselectivity (86% → 88% *ee* for **3a**). We also varied the order of addition. Our original procedure was in adding the SQ catalyst last, as noted in related conjugate additions.[10] We found an increase in *ee* if we added the catalyst *first* with **1a** (88% → 92% *ee*), indicating that precomplexation of SQ with **1a** was important *prior* to adding the nucleophile. We then moved forward to a substrate screen in which we maintained the lower temperature (−15 °C) and addition of **2** last.

We examined various aryl, heteroaryl, and alkyl *β*-nitrostyrenes (Scheme 3). The initial catalyst loading had to be

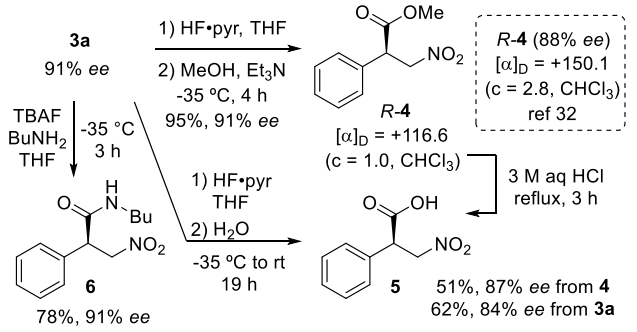
Scheme 3. Scope of *β*-Nitrostyrene Substrates



increased to 2.0 mol % to achieve full conversion within 24 h (5 mol % for alkyl derivatives). Para-substituted electron withdrawing (**3c**,**d**) and donating (**3b**,**e**) nitrostyrenes underwent the reaction with high yields and selectivities. Ortho (**3g**) or meta (**3f**) substitution did not negatively impact the selectivity. The reaction also tolerated heteroaryl nitrostyrenes with minimal impact to the enantioselectivity (pyridyl **3h** and furyl **3i**). A separate background reaction with pyridyl **1h** and **2** ascertained that the lower *ee* was due to self-catalysis from the slight basicity of the pyridyl nitrogen (∼5% conversion). Cinnamoyl **1j**, which could undergo 1,6-[22] or 1,4-addition was found to only undergo the latter (**3j**). Even branched alkyl **1k** and straight chain **1l** converted in good yield and selectivity. Substitution at the *β*-position (*β*-Me derivative of **1a**, not shown) did not react, even at 25 °C, and instead resulted in decomposition of the nitrostyrene.

Our next efforts were to unmask the TBS-MAC adduct, which generates the intermediate acyl cyanide that can be trapped as an oxidation state 3 functional group. It also allowed us to prove the absolute stereochemistry. We could scale up the reaction to yield 650 mg of product utilizing only 2 mol % SQ-IIId (**3a**, 91% *ee*, Scheme 4). Using slight modification to

Scheme 4. Unmasking and Stereochemical Determination



the procedure developed by Rawal,[10] we unmasked **3a** to form the methyl ester (**4**) in good yield while maintaining *ee* (Scheme 4). The optical rotation of **4** was the same as the Zhang group,[32] but opposite the Du group,[33] of which they determined through chemical comparison as the *S*-enantiomer (*S*-**4**), leading to our assignment as the *R*-configuration (*R*-**4**, Scheme 4). Other adducts **3b**−**3l** (Scheme 3) were assigned *R* by analogy. Nitroacid **5** was formed by saponification[34] of ester *R*-**4** using HCl with minimal loss to *ee* (91% → 87% *ee*). Attempts to unmask **3a** directly to the acid with TBAF[10,22] were not successful. However, using a similar unmasking step as the ester (HF·pyr) but quenching with water instead of MeOH/Et_3N did provide acid **5** in 62% yield, albeit with slightly lower *ee* than saponification (84% vs 87% *ee*, Scheme 4). Nitroacid **5** has been shown to be a precursor to the *β*-amino acid after hydrogenation of the nitro group.[35] Formation of amide **6** was smooth with no epimerization, following conditions similar to Nemoto's.[36]

Since the order of the addition was important to achieving higher selectivity, we propose the following mechanism in which the catalyst SQ-IIId first complexes to *β*-nitrostyrene **1a** (**7**, Figure 2). From unpublished work using Gaussian16 to find the most stable conformers of **1a** and SQ-IIId, we found single point binding of one oxygen of *β*-nitrostyrene is favored (as in **7**). We then propose that MAC **2** orients to the *re* face of **1a** where the tertiary amine is positioned for deprotonation (as in **8**), leading to adduct **9** with the anion adjacent to the NO_2 group. Proton transfer with SQ-IIId-H^+ yields the product **3a** and regenerates the catalyst. An alternative mechanism where the anion of **2** is in the catalyst pocket, as determined in the SQ-catalyzed conjugate addition of pentanedione to **1a**, cannot be ruled out without further investigation.[37]

In summary, we have developed an enantioselective conjugate addition of the masked acyl cyanide TBS-MAC to

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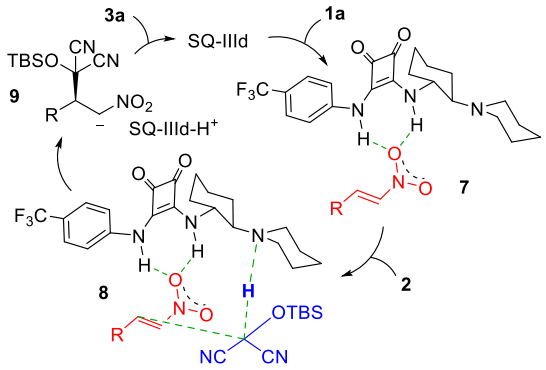

Figure 2. Proposed mechanism of the SQ-catalyzed conjugate addition of TBS-MAC **2** to β-nitrostyrene **1a**.

various aryl, heteroaryl, and alkyl β-nitrostyrenes. SQ IIId, which contains a chiral cyclohexyl piperidine, effectively promotes the reaction with low catalyst loadings through two unique modes of hydrogen bonding to produce the adducts in high yields and excellent enantioselectivities. The adducts can be unmasked to various oxidation state 3 functional groups, thereby providing an entry to the synthesis of β^2-amino acids.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c01838.

Experimental protocols, compound characterization, nuclear magnetic resonance (NMR) spectra, and chiral HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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