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# Ti(O*i*Pr)$_4$-Mediated Multicomponent Reactions Involving Triple Additions to Isonitrile Carbon Atoms

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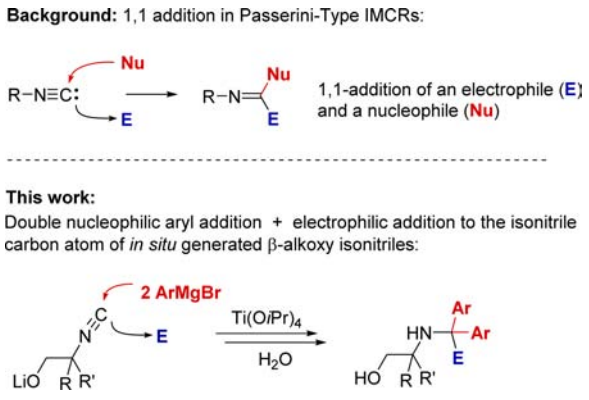
Supporting Information

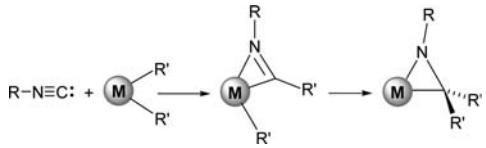
**ABSTRACT:** Double addition of Grignard reagents to isonitriles was achieved in the presence of stoichiometric amounts of [Ti(O*i*Pr)$_4$]. Functionalized isonitrile components were obtained in situ via lithiation of chiral and achiral 2-oxazolines, and the resulting amidomethyltitanium intermediate further reacted with a range of electrophiles. The established multicomponent procedure gave rise to highly substituted 2-aminomorpholines, acyclic diamino alcohols, and prenylated amino alcohols via straightforward synthetic protocols.


The rapid assembly of complex molecular target structures, such as highly substituted heterocycles, via multicomponent one-pot reactions is an attractive concept in organic synthesis.[1] Frequently, isonitriles act as key components in such transformations because of their diverse reactive potential.[2,3] The paradigm of such isonitrile multicomponent reactions (IMCRs) is the basic 1,1-addition of a nucleophile and an electrophile to the isonitrile carbon atom,[4] a reactivity pattern widely utilized in Passerini- and Ugi-type IMCRs (Scheme 1).

**Scheme 1. Reaction Pathways of Isonitriles**




The coordination of isocyanides at transition metal centers opens up additional reaction pathways for the ligated species, including nucleophilic and electrophilic additions, insertions, 1,3-dipolar cycloadditions, and reductive coupling reactions.[5] The insertion of isocyanides into metal−carbon bonds at group 4 or 5 high-valent metal centers gives rise to $\eta^2$-iminoacyl, bis($\eta^2$-iminoacyl), and $\eta^2$-imine complexes, as extensively shown by Rothwell and others.[6−8] The $\eta^2$-imine ligand at titanium(IV) could be displaced to give a free imine in high yields[7] or reacted further with an excess of alkenes or alkynes to yield five-membered azatitanacycles.[8] Notably, the $\eta^2$-iminoacyl may undergo further alkylation via insertive coupling with a second alkyl or aryl ligand or reaction with an external nucleophilic alkylation agent to give amidomethyl metal complexes ("titanaaziridines"), effectively extending the polar 1,1-addition pattern of isonitriles to a *double nucleophilic addition*:




On the basis of this organometallic reaction pattern, we developed a simple one-pot procedure for a Ti(O*i*Pr)$_4$-mediated twofold addition of aromatic Grignard reagents to the isonitrile carbon atom and subsequent trapping of the titanaaziridine with an electrophile. This protocol was then adapted for in situ-generated $\beta$-alkoxy isonitriles, which gave access to more highly functionalized targets (Scheme 1).

In a first test of the concept of a one-pot reaction based on double nucleophilic addition to isonitriles, *t*Bu-NC, 1-naphthyl-NC, and 4-methoxyphenyl-NC were reacted with [Ti(O*i*Pr)$_4$] (1.0 equiv) followed by the addition of excess Grignard reagents (3.0 equiv) as nucleophiles. Instead of the addition of an electrophile, protonolysis was initially chosen, following earlier work by Rothwell's group.[7] Aqueous quenching of the reaction intermediates gave the expected secondary amines (Scheme 2).[7,9]

We then focused on 2-lithiated 2-oxazolines, which are known to freely undergo ring-opening reactions in solution to liberate the masked isocyanide function.[10] The additional $\beta$-alkoxy group generated in the ring-opening step broadened the synthetic potential of the reaction explored above. Consecutive deprotonation of 4,4-dimethyl-2-oxazoline with a strong base and titanium-mediated arylation using the aryl Grignard

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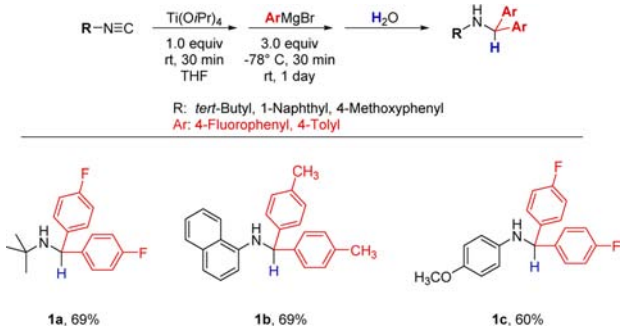
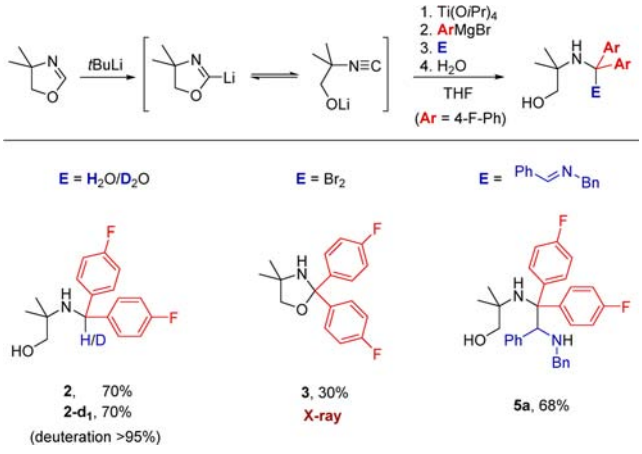
**Scheme 2. Titanium-Mediated Double 1,1-Nucleophilic Addition of Grignard Reagents to Isonitriles**




reagents in excess of the stoichiometric 2 molar equiv gave the desired diarylated amino alcohol **2** after aqueous workup (Scheme 3). The protolytic liberation of the secondary amine

**Scheme 3. Oxazolines as Masked Isonitrile Equivalents in One-Pot IMCRs**

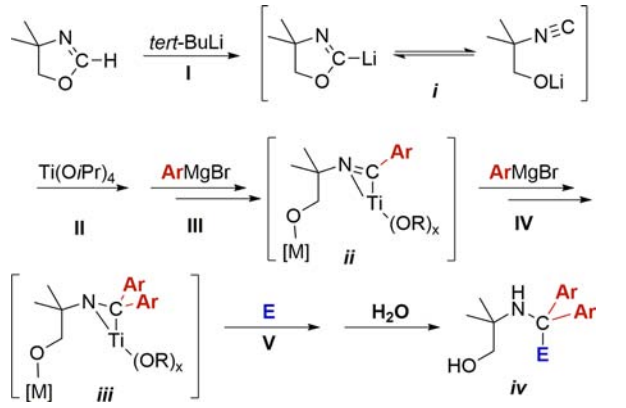



in the final step was confirmed by workup with $D_2O$, yielding quantitative deuteration of the isonitrile-derived carbon position (**2-d$_1$**; Scheme 3).

This basic reactivity pattern involving the workup of the reaction product was extended to other electrophiles. Addition of bromine to the reaction mixture obtained upon addition of the Grignard nucleophile gave the corresponding oxazolidine **3** in moderate yield, while reaction with an aromatic aldimine yielded diamino alcohol **5a** (Scheme 3). The formation of compounds **2-d$_1$**, **3**, and **5a** suggests the reaction pathway depicted in Scheme 4. First, 2-lithio-2-oxazolines (***i***, generated in step **I**) have previously been established to be present in solution in equilibrium with metalated $\beta$-alkoxy isocyanides.[10] Subsequent reaction with $[Ti(OiPr)_4]$ (step **II**) and addition of Grignard reagent yields arylated titanium species in which the coordinated isonitriles first insert into the Ti−C bonds to give iminoacyl intermediates (***ii***, step **III**), which are converted by a second insertion step (**IV**) to $\eta^2$-imine/amidomethyl complexes (***iii***), representing a titanaaziridine structural motif.[7,8] Finally, reaction with the electrophile E and/or hydrolysis (step **V**) gives rise to the amino alcohol derivatives (***iv***), which may be isolated.

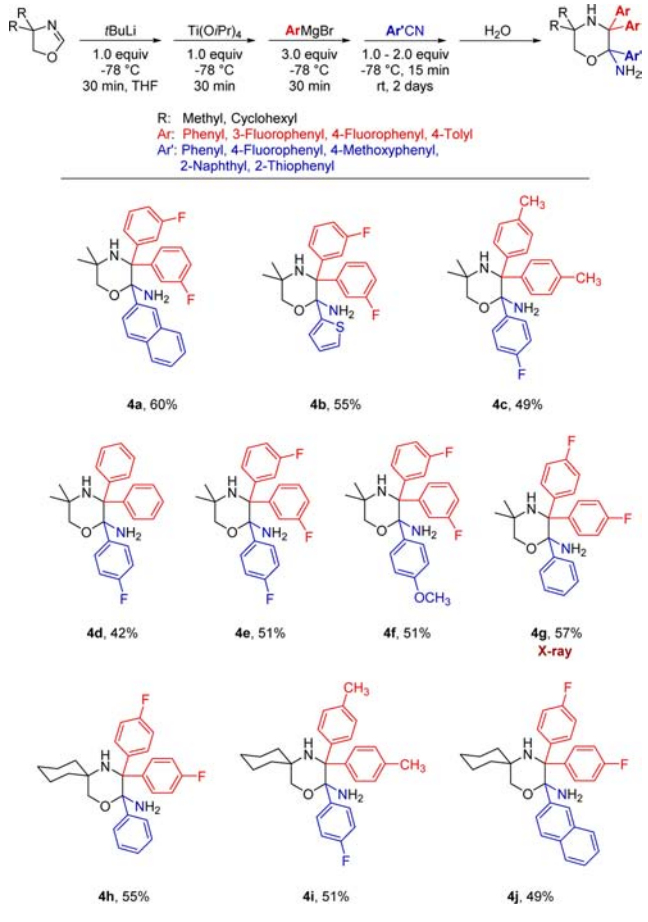
The reaction with different electrophiles within the established one-pot procedure was further investigated to assess the potential of these multicomponent transformations

**Scheme 4. Proposed Reaction Pathway for the Ti-Mediated IMCR**




in the synthesis of highly functionalized target structures. First, the reaction of 4,4-dimethyl-2-oxazoline and 3-oxa-1-azaspiro[4.5]dec-1-ene with a range of aryl magnesium reagents and aromatic nitriles as electrophiles was investigated (Scheme 5). Upon hydrolytic workup, this transformation directly gave cyclized morpholine derivatives containing three aromatic substituents and primary and secondary amino groups. Following an optimized one-pot protocol, the consecutive addition of *tert*-butyllithium (1.0 equiv), $[Ti(OiPr)_4]$ (1.0 equiv), an aromatic Grignard reagent (3.0 equiv), and an

**Scheme 5. 2-Aminomorpholines: Reaction Scope of Aromatic Grignard Reagents and Aromatic Nitriles**



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aromatic nitrile (1.0−2.0 equiv) to a cooled THF solution of a 4,4-dialkyl-2-oxazoline gave the expected 2-aminomorpholines **4a−j** (Scheme 5). Notably, alkyl Grignard reagents did not lead to analogous products in this multicomponent synthesis. As observed in the test reactions described above, the arylations using organomagnesium reagents took place only in the presence of stoichiometric amounts of $[Ti(OiPr)_4]$.[11] For compound **4g** a single-crystal X-ray structure analysis confirmed the structural assignment and established the details of the molecular structure (Figure 1). The morpholine ring adopts a chair conformation with the primary amino substituent occupying an axial position.

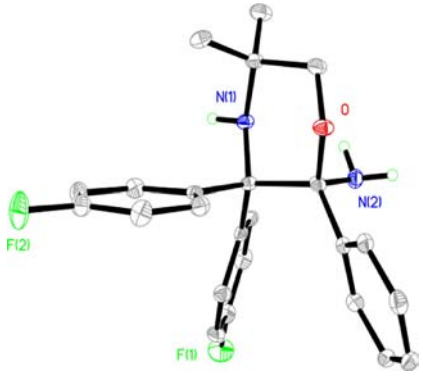


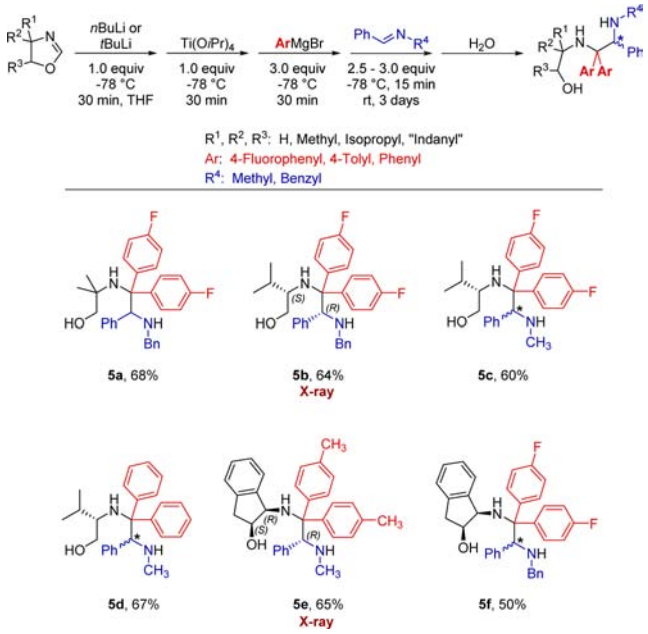

**Figure 1.** Molecular structure of **4g**, with thermal ellipsoids set at the 50% probability level. H atoms, except *N*-H atoms, have been omitted for clarity. For selected bond lengths and angles, see the Supporting Information.

The addition of aromatic aldimines as electrophiles, already tested in the exploratory work represented in Scheme 3, was then further investigated. The observed reactivity pattern is consistent with an insertion of the aldimine C═N unit into the titanium−carbon bond of the hypothesized intermediate titanaaziridine species (*iii* in Scheme 4). The expected acyclic diamino alcohols **5a−f** were isolated following the general one-pot procedure (Scheme 6). These compounds contain a newly formed tertiary stereocenter at the former imine carbon atom. Notably, only one diastereoisomer was isolable as the main product of each reaction, while a potential minor diastereomer was not observed. The absolute configurations of compounds **5b** (Figure 2) and **5e** were determined by single-crystal X-ray structure analysis.

In addition to the straightforward insertion reactions of aldimines and nitriles into early transition metal−carbon bonds, pericyclic rearrangements of titanacycles and allylic alkoxides have only recently been established as a general tool for synthetically useful C−C couplings.[12] This type of reactivity has been studied in detail by Micalizio and co-workers and may also be viewed as indirect evidence for the presence of in situ-formed reactive titanacycles. The established oxazoline deprotonation−arylation sequence was thus combined with a subsequent reaction with a separately generated allylic alkoxide. After workup the expected prenylated amino alcohols **6a−c** were obtained in moderate yields (Scheme 7).

In this first study, the one-pot multicomponent syntheses of functionalized 2-aminomorpholines, acyclic diamino alcohols, and prenylated amino alcohols mediated by $[Ti(OiPr)_4]$ have been developed, starting from 2-lithiated 2-oxazolines, aromatic Grignard reagents, and different unsaturated electrophiles. A

**Scheme 6. Acyclic Diamino Alcohols: Reaction Scope of Aromatic Grignard Reagents and Aromatic Aldimines**



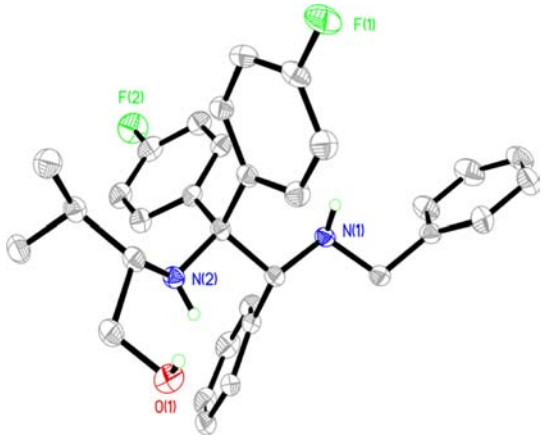
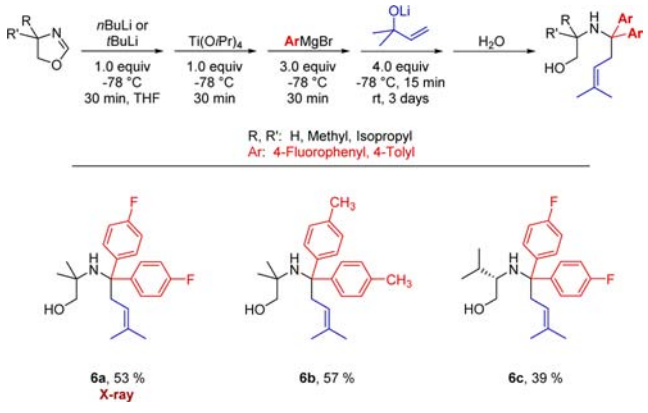




**Figure 2.** Molecular structure of **5b**, with thermal ellipsoids set at the 50% probability level. H atoms, except *N*-H and *O*-H atoms, have been omitted for clarity. For selected bond lengths and angles, see the Supporting Information.

**Scheme 7. Prenylated Amino Alcohols: Reaction Scope of Aromatic Grignard Reagents and Allylic Alkoxides**



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common reaction pathway for these reactions is proposed to be based on the double insertion of an isonitrile unit into Ti−C bonds, giving rise to titanaaziridine species as key intermediates.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02746.

Detailed experimental procedures, characterization data, and NMR spectra (DOC)
X-ray data for **3**, **4g**, **5b**, **5e**, and **6a** (CIF)

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### Author Contributions

#These authors contributed equally to this work.


### Notes

The authors declare no competing financial interest.

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