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Catalytic α-Monoallylation of Aryl Acetonitriles

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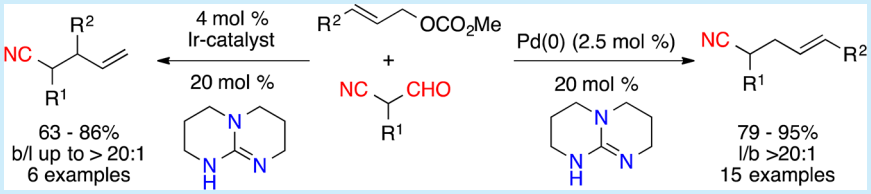
Supporting Information



ABSTRACT: α-Cyano aldehydes undergo selective transition-metal-catalyzed monoallylation to provide α-allylated nitriles. The transformation leads to linear substitution products with palladium catalysts or branched allylated nitriles using an iridium catalyst. Facile TBD-catalyzed retro-Claisen cleavage is leveraged to attain selective monoallylation.

Transition-metal-catalyzed Tsuji–Trost-type allylation of stabilized nucleophiles is a powerful method for carbon–carbon bond formation.[1] While the allylation of stabilized malonate nucleophiles has received significant attention, somewhat less attention has been paid to nitrogen-containing carbon nucleophiles. Given the preponderance of nitrogen-containing biologically active molecules, we are interested in developing methods that allow facile incorporation of nitrogen via transition-metal-catalyzed allylation reactions.

The versatility of nitriles, which can be rapidly transformed to amides and amines,[2] has motivated development of α-allylation of nitriles by decarboxylative allylation.[3,4] These reactions often lead to quaternary carbon centers, thus obviating problems with overallylation.[3a] In contrast, the α-monoallylation of nitriles to form tertiary carbon centers is challenging due to competing overallylation and protonation reactions.[5,6]

To achieve selective α-monoallylation of nitriles, we envisioned that a carbonyl functional group α to a nitrile group would (A) activate the substrate toward Tsuji–Trost allylation and (B) act as a blocking group to prohibit overallylation (Scheme 1). Moreover, it was anticipated that the carbonyl group could be removed in situ via retro-Claisen condensation.

Our preliminary studies focused on the treatment of α-cyano aldehyde **1a** with cinnamyl carbonate **2a** in the presence of catalytic $Pd(PPh_3)_4$ and amine (Table 1). In each case, selective monoallylation was achieved. However, triazabicyclodecene (TBD) proved to be the best catalyst, smoothly giving rise to the corresponding allylated product **3a** within 30 min (Table 1, entry 5).

Scheme 1. Retro-Claisen Allylation Concept

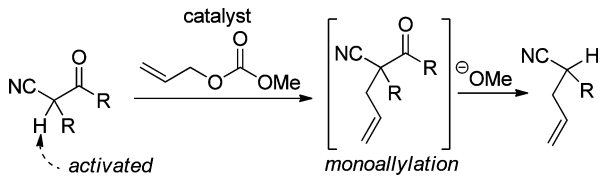
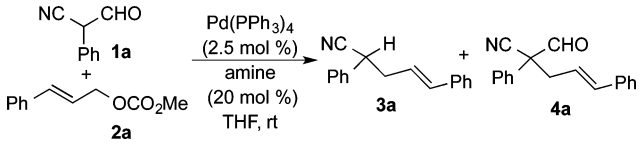
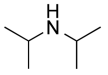
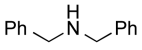
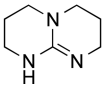


Table 1. Amine Screening



2a **3a** **4a**

entry	co-catalyst	time (h)	yield (%)[a] 3a:4a
1		2.0	73:0
2		2.0	45:8
3		2.0	52:2
4		2.0	64:0
5		0.5	95:0

[a]Isolated yield after purification by column chromatography on SiO_2.

Using **1a** and **2a** as representative substrates, a series of control experiments were performed. Exclusion of $Pd(PPh_3)_4$ catalyst did not yield any product, whereas exclusion of TBD

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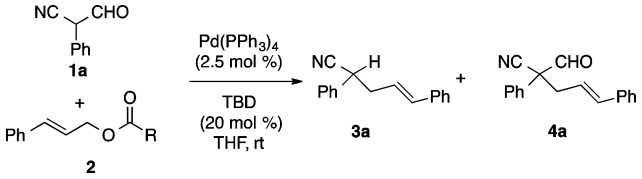
yielded **3a** (15%) and the allylated aldehyde **4a** (22%) after extended reaction time (16 h). Thus, TBD is necessary for rapid allylation and retro-Claisen cleavage of the aldehyde.

The choice of allyl methyl carbonate as allylating agent was also crucial to promote the retro-Claisen condensation to form **3**. Employment of allylic acetates as allylating agents yielded the aldehyde product **4a** as the major product (Table 2, entry 1),

Table 2. Allylating Agents



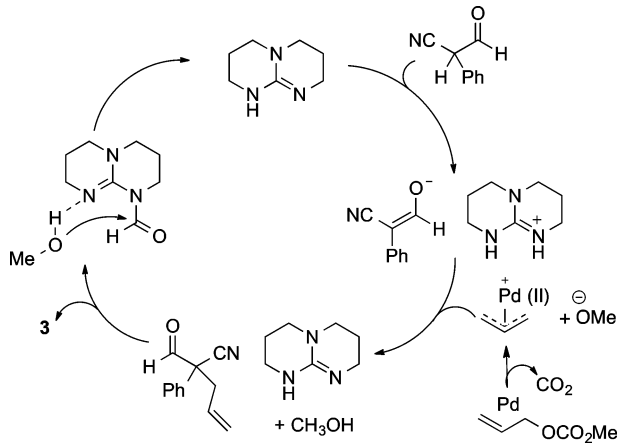
entry	allylating reagent, **2**	time (h)	yield (%)[a] **3a**/**4a**
1	R = CH_3	14	22:58
2	R = O^{t}Bu	14	63:18
3	R = OCH_3	0.5	95:0

[a]Isolated yield after purification by column chromatography on SiO_2.

whereas use of allyl *tert*-butyl carbonate provided a mixture of **3a** and **4a**. Only use of allyl methyl carbonate exclusively yielded the product of retro-Claisen cleavage (**3a**) in high yield in a short reaction time.

Mechanistically, we propose that the allylation reaction involves two synergistic catalytic cycles (Scheme 2). The TBD

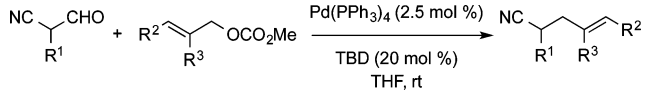
Scheme 2. Potential Mechanism

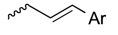
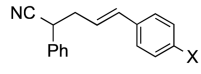
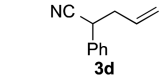
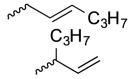
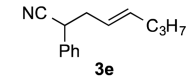
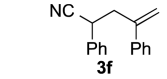
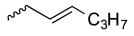
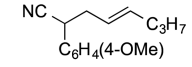
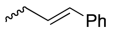
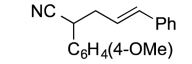
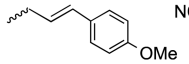
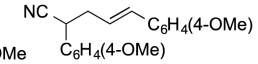
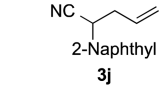
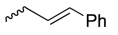
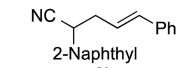
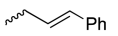
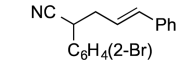
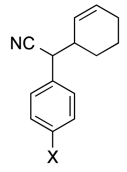
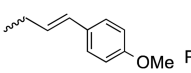
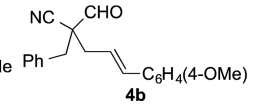


catalyst likely acts as a general base to generate the stabilized carbanion nucleophile.[7] This nucleophile undergoes catalytic allylation. Finally, to explain why rapid retro-Claisen cleavage requires both methyl carbonate and TBD, we propose that TBD catalyzes the cleavage of the aldehyde with methanol.[8] Such a proposal is consistent with the proposed mechanism for TBD-catalyzed transesterifications.[9]

A representative range of allylic carbonates participated in the deformylative allylation (Table 3, entries 1–7 and 14). Substitution of the aromatic ring of cinnamyl carbonate showed that electron-deficient carbonates react more slowly than electron-rich allyl carbonates, although the magnitude of the effect is relatively small (entries 2 and 3). Alkyl carbonates also underwent efficient coupling, with both primary and secondary alkyl carbonates providing the linear allylation product (97:3, entries 5 and 6). Substitution of the aromatic ring α to the

Table 3. Palladium-Catalyzed Allylation[a]



entry	allyl carbonate	product	time (h)	yield (%)[b]
1		 **3a** X = H	0.5	95
2		**3b** X = OMe	1.0	80
3		**3c** X = NO_2	5.0	85
4		 **3d**	1.0	89
5		 **3e**	1.0	89[c]
6			2.0	87[c]
7		 **3f**	5.0	93
8		 **3g**	1.5	86[d]
9		 **3h**	1.0	83
10		 **3i**	1.0	84
11		 **3j**	2.0	79
12		 **3k**	1.0	83
13		 **3l**	1.0	87
14		 **3m** X = H	2.0	89[e]
15		**3n** X = OMe	1.5	83[e]
16		 **4b**	16.0	57

[a]Reaction conditions: cyano aldehyde (1.0 equiv), reagent (1.1 equiv), $Pd(PPh_3)_4$ (2.5 mol %), TBD (20 mol %), THF, rt. [b]Isolated yield after purification by column chromatography on SiO_2. [c]Linear/branched = 97:3. [d]Linear/branched = 96:4. [e]Diastereomeric ratio (dr = 1:1) was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

nitrile was also tolerated (entries 8–13 and 15). Importantly, allylic alkylation is faster than the oxidative addition to a brominated arene (entry 13). Unfortunately, under the same reaction conditions, α-aliphatic nitrile substrates gave the allylated aldehyde, which did not undergo in situ retro-Claisen

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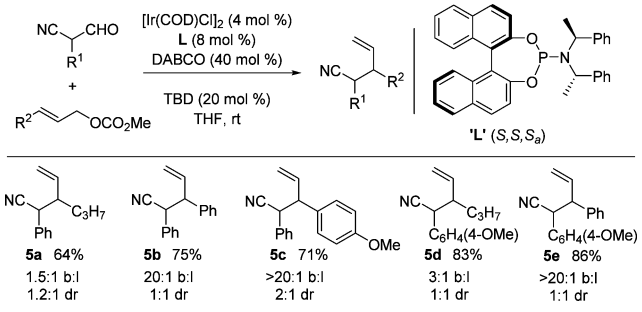
cleavage to give the protonated product even after elongated reaction time (entry 16).

To extend this protocol further, we envisioned that the method would yield branched allylated product by tuning the transition metal catalyst. While nucleophilic addition to the less hindered position of allylic electrophiles is typically favored by palladium catalysts,[1] branched substituted products are often favored by Mo, Ru, Rh, and Ir catalysts.[10]

Thus, we also examined the analogous reaction of nitriles in the presence of an Ir catalyst, which forms the branched product regioselectively with a range of allylic electrophiles. For example, in the presence of 4 mol % of $[Ir(COD)Cl]_2$, 8 mol % of ligand **L**,[11,12] and 40 mol % of DABCO, cyano aldehydes **1a,b** smoothly underwent the allylation in THF at room temperature to afford moderate to high regioselectivity in favor of branched products (Scheme 3). The reaction proceeded well

Scheme 3. Iridium-Catalyzed Allylation

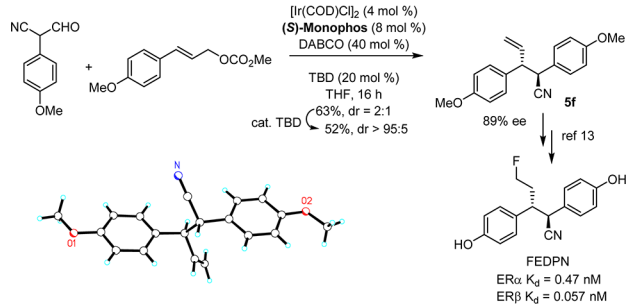


at room temperature, albeit with longer reaction times (15−26 h) as compared to the palladium-catalyzed reactions. Higher temperatures resulted in complicated reaction mixtures.

Interestingly, the reaction without DABCO did not provide any product, which might be due to the improper in situ formation of the active Ir catalyst.[12] Varying the substitution on the aromatic moiety of the pro-nucleophile does not have a remarkable effect on regioselectivity (cf. Scheme 3, **5b** and **5e**), whereas the branched to linear selectivity changes significantly with changes to the substituent on the allyl carbonate electrophile. In identical reaction conditions, aromatic allyl carbonates provided good to excellent branched selectivities (Scheme 3, **5b**, **5c**, and **5e**) in comparison to aliphatic allyl carbonates which provided much lower selectivities (Scheme 3, **5a** and **5d**). Using the optically active (S,S,S_a) phosphoramidite ligand allowed the synthesis of **5c** in 62% ee (major diastereomer) and **5e** in 58% ee. The low dr coupled with the modest enantioselectivities was somewhat discouraging. However, in our pursuit of a synthesis of an estrogen receptor inhibitor (FEDPN),[13] it was noted that the presence of an electron-donating methoxy group on both the pro-electrophile and pro-nucleophile produced more highly enantioenriched product (89% ee). However, the product was formed as a 2:1 mixture of diastereomers (Scheme 4). Gratifyingly, epimerization with TBD in EtOAc/hexane solvent allowed selective dynamic crystallization to form a single diastereomer of **5f** in acceptable yield and good ee (52%, 89% ee).[14] The *anti* stereochemistry was confirmed by X-ray crystallographic analysis.[15]

In conclusion, we have developed a conceptually new and operationally simple catalytic system for the monoallylation of nitriles. The method utilizes an aldehyde to activate nitriles toward α-allylation and prevent multiple allylations. After

Scheme 4. Asymmetric Allylation and Dynamic Crystallization



allylation, a facile in situ retro-Claisen cleavage of the activating/blocking group provides the monoallylated nitriles. The regiochemistry of allylation can be controlled by the choice of catalyst, with Pd providing the linear allylation products and an Ir catalyst giving the branched products. Lastly, use of an enantiopure Ir-phosphoramidite catalyst leads to enantioselective allylation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds and a CIF file for compound **5f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) Hammar, P.; Ghobril, C.; Antheaume, C.; Wagner, A.; Baati, R.; Himo, F. *J. Org. Chem.* **2010**, *75*, 4728.
(8) (a) Methoxide, generated from decarboxylation of methyl carbonate, likely rapidly deprotonates TBD-H^+. Relevant pK_a values: TBD 26 in CH_3CN; MeOH 29 in DMSO; NCCH(Me)Ph 23 in DMSO. (b) Rodima, T.; Kaljurand, I.; Pihl, A.; Maemets, V.; Leito, I.; Koppel, A. I. *J. Org. Chem.* **2002**, *67*, 1873. (c) Kaljurand, I.; Kutt, A.; Soovali, L.; Rodima, T.; Maemets, V.; Leito, I.; Koppel, A. I. *J. Org. Chem.* **2005**, *70*, 1019.
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(15) CCDC-912361 contains the supplementary crystallographic data for the major isomer of **5f**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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