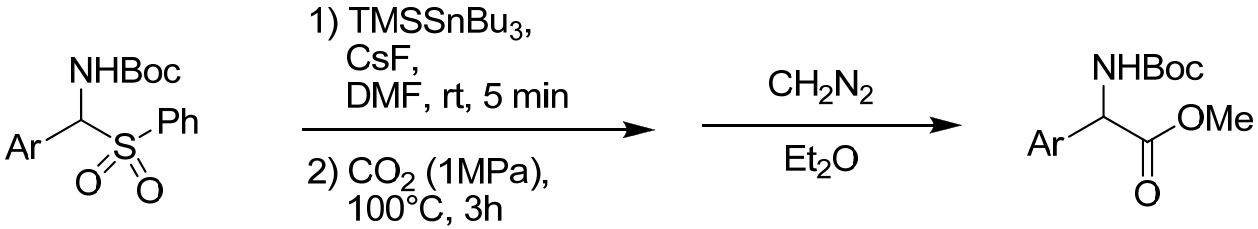
One-Pot Synthesis of α-Amino Acids from Imines through CO_2 Incorporation: An Alternative Method for Strecker Synthesis

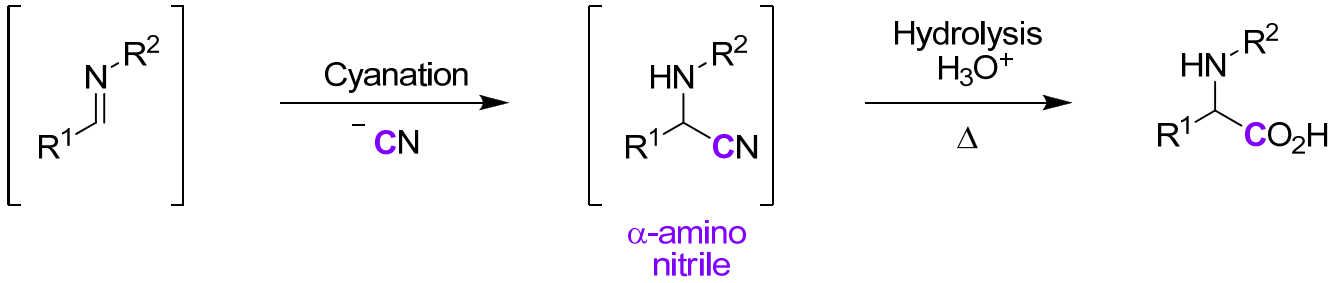


Tsuyoshi Mita, Jianyang Chen, Masumi Sugawara and Yoshihiro Sato

Angew. Chem. Int. Ed., **2010**, *49*, Early view

Synthetic strategies for α-amino acids from imines

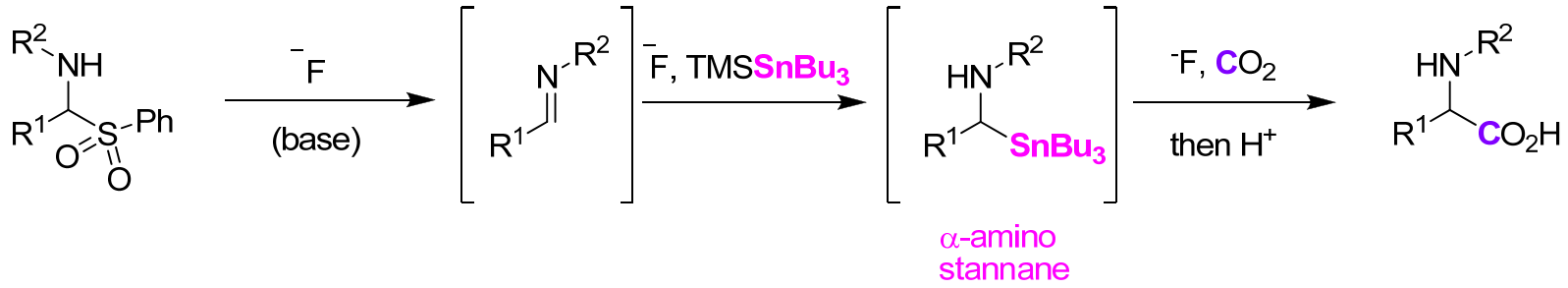
Classical method: Strecker synthesis



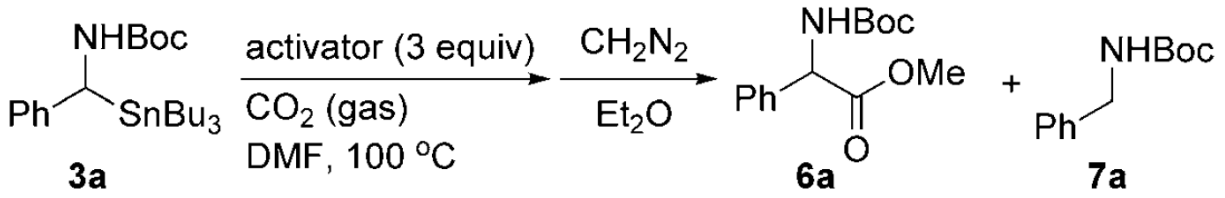
➡ This method has some pratical drawbacks :

- The use of highly toxic hydrogen cyanide or an alkali metal cyanide or TMSCN.
- The need for hydrolysis in strongly acidic media at a high temperature

Their work: replacement of cyanide by CO_2 and reversal of polarity on the imino central carbon atom by the use of stannyl anion.



Investigation of carboxylation using various fluoride sources.

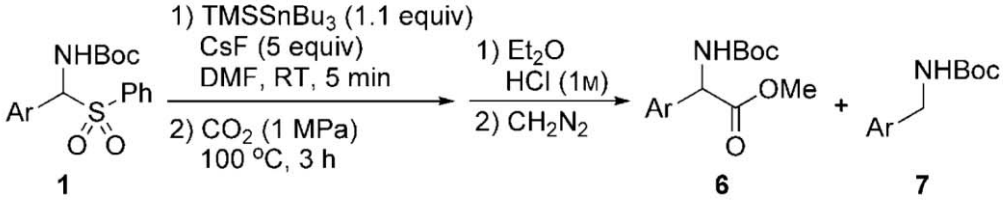


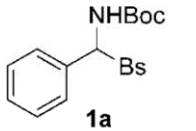
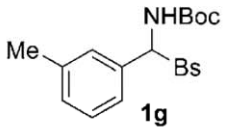
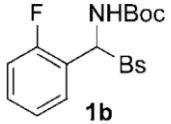
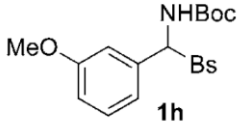
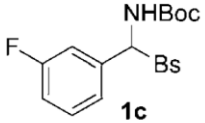
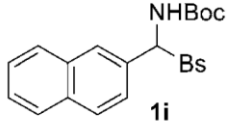
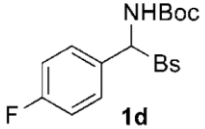
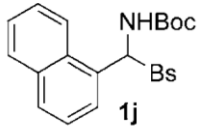
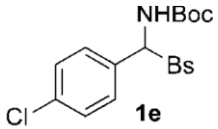
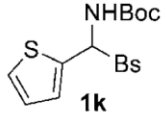
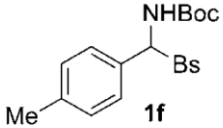
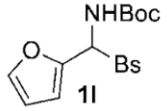
Entry	Activator	CO_2 [MPa]	t [h]	Yield [%][a]		
				6a	**7a**	**3a**
1	LiF	0.1 (1 atm)	12	–	2	98
2	NaF	0.1	12	–	3	97
3	KF	0.1	12	10	9	59
4	KF + [18]crown-6	0.1	12	22	30	15
5[b]	CsF	0.1	3	62 (60)	21	7
6[b]	CsF	0.5	3	84 (71)	2	4
7[b]	CsF	1	3	86 (75)	<1	–
8[b]	TBAT	1	3	49	1	10

[a] Yields were determined by using ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. The values in parentheses represent the yields of isolated product. [b] The reaction was performed at 110 °C. TBAT = Tetrabutylammonium triphenyldifluorosilicate.

One-pot synthesis of α-amino acids

Table 2: One-pot synthesis of α-amino acids.

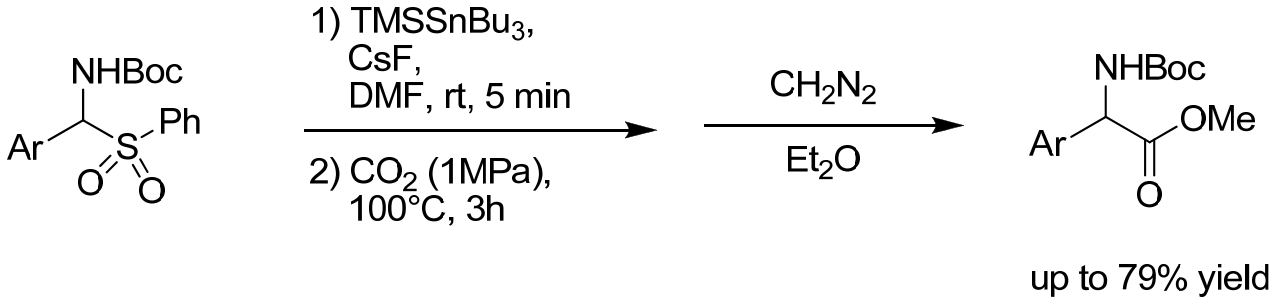


Entry	Substrate	Yield [%][a] 6	7	Entry	Substrate	Yield [%][a] 6	7
1	 **1a**	81 (78)	7				
2[b]		28	36	8[d]	 **1g**	74 (57)	8
3	 **1b**	61 (52)	12	9	 **1h**	88 (79)	8
4	 **1c**	62 (46)	19	10	 **1i**	73 (66)	15
5	 **1d**	79 (63)	11	11	 **1j**	65 (62)	14
6	 **1e**	64 (51)	17	12	 **1k**	49 (46)	8
7[c]	 **1f**	53 (47)	6	13[e]	 **1l**	62 (55)	6

[a] Yields were determined by using ^{1}H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. The values in parentheses represent the yields of isolated product. [b] Imine **2a** was used as a substrate and 7% of benzaldehyde was formed. [c] 9% of α-amino stannane **3f** remained. [d] 3% of α-amino stannane **3g** remained. [e] The reaction was performed at 110 °C. Bs = benzenesulfonyl.

Conclusion

Novel One-pot process for the synthesis of α-amino acids from imine equivalents using CO_2 gas as a carbon source.



Three successive reactions (imine formation, stannylation, and carboxylation) proceed in the same flask

Fluoride source CsF plays a different role for each step