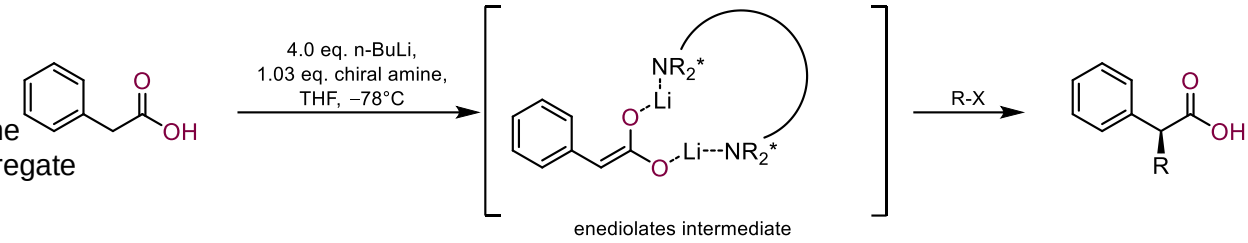
METHOD of the week: Enantioselective α-Alkylation of Carboxylic Acid

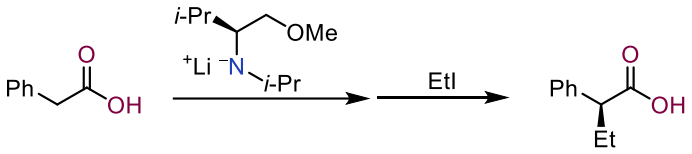
The SARLAH Group

- Asymmertic environment generated by preorganized enediolates
- C2-symmetric chiral tetraamine
- Spectroscopic and computational support the asymmertic environment of anion-lithio aggregate
- Recyclable ligand no further operation after alkylation
- Stoichiometric amount ligand/BuLi



Zakarian et al. J. Am. Chem. Soc. **2011**, *133*, 31, 11936–11939. https://doi.org/10.1021/ja205107x

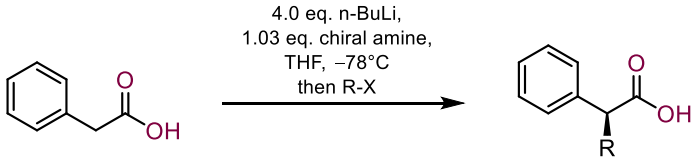
First Reported of Enantioselective α-Alkylation of Carboxylic acid



Lithiation Temp.	Alkylation Temp.	Electrophile	ee (%)	Isolation yield (%)
-10°C	-70°C	EtI	0	39
-45°C	-70°C	Eti	0	51
-70°C	-70°C	EtI	8	82
-70°C	-70°C	EtBr	12	22
-90°C	-90°C	EtI	24	18

Shioiri et al. Chem. Commun **1987**, 656– 658. . https://doi.org/10.1039/C39870000656

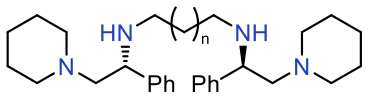
Reaction Optimization



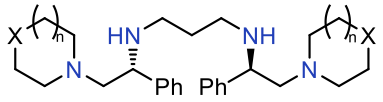
control experiemnt	ee (%)	conversion (%)
n-BuLi (4 eq.), **1** (0.9 eq.)	67	88
n-BuLi (4 eq.), **1** (1.03 eq.)	93	91
n-BuLi (4 eq.), **1** (2.05 eq.)	75	89
n-BuLi (2 eq.), **1** (1.05 eq.)	0	88
n-BuLi (4 eq.), **1** (1.03 eq.), *n*-BuOLi(1 eq.)	52	48
n-BuLi (4 eq.), **1** (1.03 eq.), LiBr(1 eq.)	9	23

Zakarian et al. J. Am. Chem. Soc. **2011**, *133*, 31, 11936–11939. https://doi.org/10.1021/ja205107x

Ligand Screening



		ee
1	n=0	7% ee
	n=1	93% ee
	n=2	0% ee

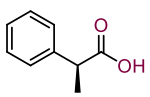


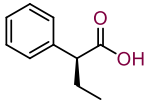
			ee
1	X=C	n=0	65%
	X=C	n=1	93%
	X=C	n=2	66%
	X=O	n=0	90%

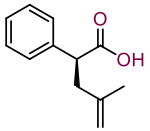
- Aged bottle of BuLi didn't erode the ee and yield
- Equivalent should be control carefully
- The spacer between two secondary is very important
- The ring size of the tertiary amine is also important
- The morpholine ring also give good ee

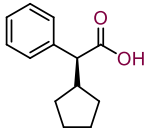
Enantioselective α-Alkylation of Carboxylic Acid

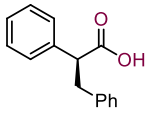
Scope of R-X

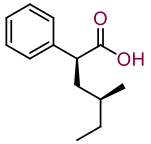

83%
88% ee

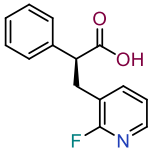

81%
96% ee

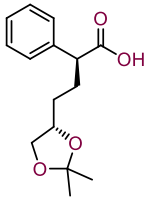

80%
91% ee


76%
96% ee

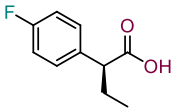

85%
92% ee

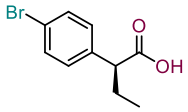

67%
99% d.r.

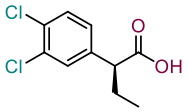

91%
93% ee

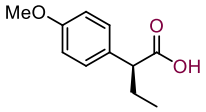

74%
91% d.r.

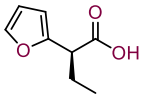
Scope of Carboxylic acid

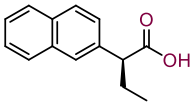

84%
96% ee

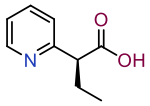

65%
93% ee

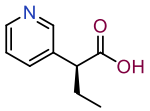

82%
92% ee


71%
89% ee


60%
97% ee

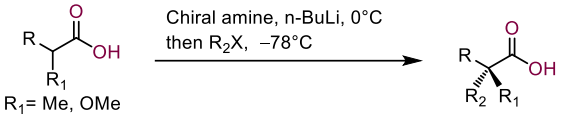

88%
96% ee

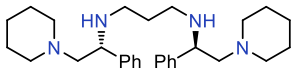

12%
0% ee

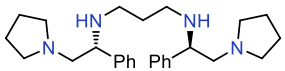

61%
95% ee

Zakarian et al. J. Am. Chem. Soc. **2011**, *133*, 31, 11936–11939. https://doi.org/10.1021/ja205107x

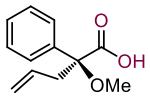
Tetrasubstituted α-Stereocenter- Alkylation

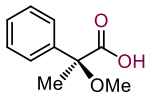


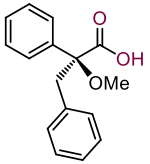

1

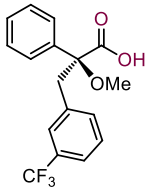

2

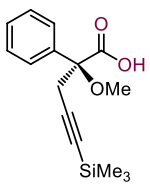
Scope of R_2-X

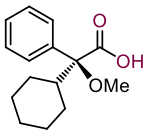

1 78%, 83% ee
2 79%, 89% ee


1 77%, 97% ee
2 78%, 93% ee

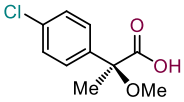

2 70%, 94% ee

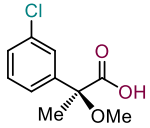

2 89%, 84% ee

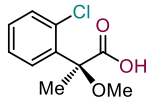

2 72%, 89% ee

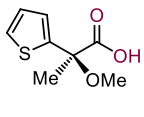

1 70%, 88% ee
2 69%, 91% ee

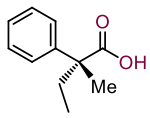
Scope of Carboxylic acid

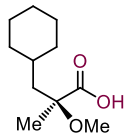

1 84%, 90% ee


1 69%, 84% ee


1 68%, 75% ee
2 70%, 94% ee


1 84%, 88% ee
2 80%, 94% ee


1 72%, 90% ee

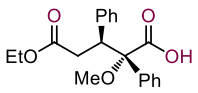

1 66%, 85% ee

Zakarian et al. J. Am. Chem. Soc. **2017**, *139*, 1, 527–533. https://doi.org/10.1021/jacs.6b11673

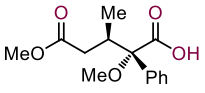
Enantioselective α-Alkylation of Carboxylic Acid

Tetrasubstituted α-Stereocenter- Conjugated Addition

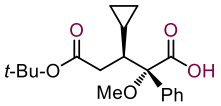
Scope of unsaturated ester



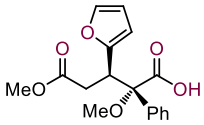
1 77%, 96% ee
dr > 30:1



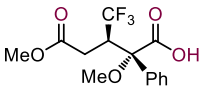
1 84%, 95% ee
dr > 30:1
4.1 g scale
98% recovery of ligand



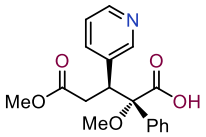
1 86%, 97% ee
dr > 30:1



1 58%, 98% ee
dr > 30:1

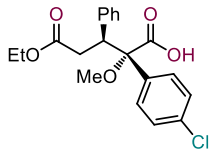


1 66%, 95% ee
dr > 30:1

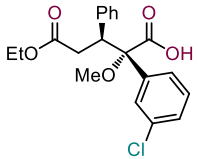


1 55%, 93% ee
dr > 30:1

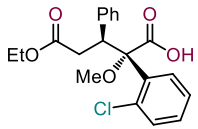
Scope of unsaturated ester



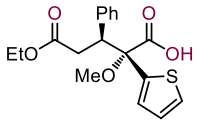
1 79%, 91% ee
dr > 30:1



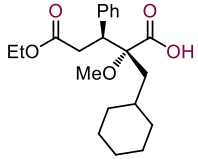
1 54%, 86% ee
dr > 30:1



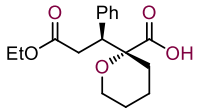
1 47%, 78% ee
dr = 10:1



1 66%, 97% ee
dr > 30:1



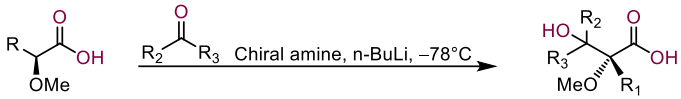
1 67%, 98% ee
dr = 10:1

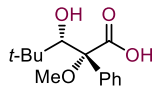


1 74%, 98% ee
dr > 30:1

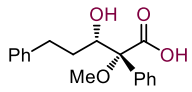
Zakarian et al. J. Am. Chem. Soc. **2011**, *133*, 31, 11936–11939. https://doi.org/10.1021/ja205107x

Tetrasubstituted α-Stereocenter- Aldol Reaction

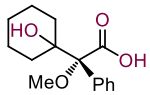




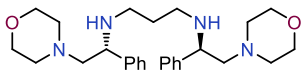
1 60%, 50% ee, dr = 10:1
2 64%, 89% ee, dr = 13:1



1 51%, 80% ee, dr = 1.5:1
2 52%, 71% ee, dr = 1:1

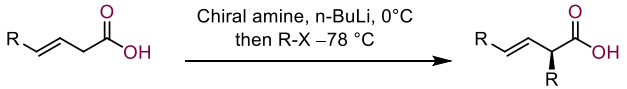


1 84%, 80% ee
2 88%, 71% ee
3 68%, 80% ee

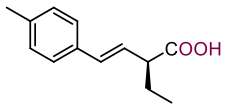


3

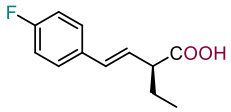
α-Alkylation of β,γ – Unsaturated Acid



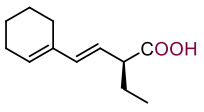
Scope



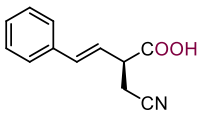
96:4 er, α:γ > 20:1
83 %



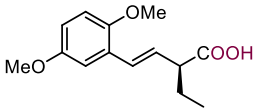
95:5 er, α:γ = 16:1
69 %



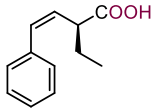
95:5 er, α:γ > 20:1
94 %



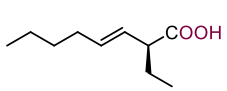
73:27 er, α:γ > 20:1
90 %



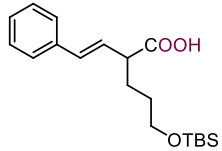
97:3 er, α:γ = 8:1
80 %



57:43 er, α:γ > 20:1
48 %



88:12 er, α:γ > 20:1
67 %



89:11 er, α:γ = 5:1
63 %

Zakarian et al. J. Am. Chem. Soc. **2011**, *133*, 31, 11936–11939. https://doi.org/10.1021/ja205107x

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