別紙４－２（課程博士（和文））

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| 応用化学・生命工学専攻 | 学籍番号 | 第 141816 号 |
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# 論文内容の要旨（博士）

| 博士学位論文名 | カルボキシ基の脱炭酸反応を利用したハロゲン系官能基の導入反応 |
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（要旨　1,200 字程度）

カルボン酸は天然に広く存在し、入手容易な化合物として知られる。カルボン酸を一段階で合成変換できる脱炭酸反応は有用な分子変換反応として精力的に研究されてきた。しかし、脱炭酸反応は強固な炭素―炭素結合を切断する必要があるため、高価な遷移金属触媒や厳しい反応条件が必要な点が課題である。一方、β位にカルボニル基を有するβ－オキソカルボン酸はカルボニル基の共鳴安定化効果により温和な条件で脱炭酸が進行する。この性質を利用した反応は近年盛んに研究されているが、第三級β－オキソカルボン酸を反応基質とした脱炭酸的官能基化反応の報告例は非常に少ない。筆者の所属する研究室では最近、第三級β－オキソカルボン酸の不斉脱炭酸的塩素化反応および触媒を用いない脱炭酸的フッ素化反応を報告している。私はこれら研究で得られた知見を用いて第三級カルボン酸の脱炭酸的官能基化反応の適用範囲の拡大やα－ハロケトンの誘導化反応について研究を行った。

はじめに、２－ピリジル酢酸リチウム塩の脱炭酸的官能基化反応に関する研究を行った。２－ピリジル酢酸は脱炭酸後に生じるカルバニオンが共鳴安定化される事により容易に脱炭酸を起こすが、この現象を官能基化反応に応用した例はほとんど報告されていない。筆者はピリジル酢酸のリチウム塩に対してSelectfluorを作用させる事でフッ素化反応が円滑に進行する事を見出した。またエステルのけん化と続く脱炭酸的フッ素化反応を同一フラスコで実践する手法についても検討し、２段階で86%収率と良好な収率で目的物を得た。トリフルオロメチルチオ化反応についても検討を行った。トリフルオロメチルチオ基は近年、医薬品開発分野において注目を集める部分構造である。筆者は求電子的トリフルオロメチルチオ化剤存在下、２－ピリジル酢酸リチウム塩を反応させる事でトリフルオロメチルチオ化体が良好な収率で得られる事を見出した。

また、第三級β－ケトカルボン酸の脱炭酸的アルドール反応が円滑に進行する事も見出した。上述の通り第三級β－オキソカルボン酸の脱炭酸的官能基化反応はこれまでほとんど報告されてこなかったが、強力な求電子的アルドール受容体であるトリフルオロピルビン酸エステル存在下であれば、円滑にアルドール反応が進行する事が明らかとなった。またキラルアミン触媒存在下で反応を行ったところ良好な収率、ジアステレオ選択性および中程度から良好なエナンチオ選択性で目的のアルドール付加体が得られた。

続いて、パラジウム触媒を用いたβ－ケトアリルエステルの脱炭酸的フッ素化反応に関する研究を行った。β－ケトアリルエステルの遷移金属触媒による脱炭酸的アリル化反応は古くから知られているが、同反応をアリル化以外の官能基化反応に応用した例はほとんど報告されていない。筆者は脱炭酸後に生じるπ－アリルエノラート中間体に求電子的フッ素化剤を作用させる事でフッ素化反応が進行するのではないかと考えた。溶媒としてEtOH、配位子としてBINAPを用いる事で収率が大幅に向上し、目的のα－フルオロケトンを高収率で得た。

最後にスピロ環化合物の誘導化反応を行った。筆者の所属する研究室では側鎖末端に求核剤を有するα－クロロケトンの$S_N2$反応により多環式化合物が得られる事を報告している。筆者は得られたキラル多環式化合物の誘導化反応を着想した。エーテル化反応やフリーデル・クラフツ反応、水素添加反応を行い、良好なジアステレオ選択性および収率で目的物が得られた。

別紙４－１（課程博士（英文））

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# Abstract（Doctor）

| Title of Thesis | Introduction of halogen-containing functional groups by decarboxylation reaction of carboxylic acids |
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Approx. 800 words


Carboxylic acids are abundant and widely available compounds. Therefore, decarboxylation reactions that can functionalize carboxylic acids in a single step have been studied intensively as highly useful reactions in organic chemistry. However, decarboxylation reactions generally require harsh conditions or expensive transition-metal catalysts to cleave the strong carbon–carbon bond. In contrast, β-oxocarboxylic acids decarboxylate easily due to the resonance stabilizing effect of the adjacent carbonyl groups. Recently, there has been considerable research on the decarboxylative functionalization of β-oxocarboxylic acids such as via Mannich and aldol reactions; however, reports on decarboxylative functionalization using tertiary β-oxocarboxylic acids are limited. Our research group recently reported the enantioselective decarboxylative chlorination of tertiary β-ketocarboxylic acids using a chiral primary amine catalyst, and the catalyst-free decarboxylative fluorination of β-ketocarboxylic acids. Based on this work, the expansion of the substrate scope of the decarboxylative functionalization of tertiary carboxylic acids and derivatization of α-haloketone derivatives were investigated in this study.

Catalyst-free decarboxylative functionalization of lithium 2-pyridylacetate is described in chapters 2 and 3. 2-Pyridylacetic acid undergoes decarboxylation as easily as β-ketocarboxylic acids owing to the resonance stabilization from the delocalization of the carbanion into the pyridine ring. However, there are very few reports on the application of this phenomenon to the decarboxylative functionalization of 2-pyridylacetic acid in the absence of transition-metal catalysts. Additionally, because fluorine is prevalent in pharmaceuticals and pesticides, the development of fluorination reactions is important. Therefore, the decarboxylative fluorination of 2-pyridylacetic acid was proposed.

First, lithium 2-pyridylacetate was synthesized from methyl 2-pyridylacetate by saponification. The treatment of lithium 2-pyridylacetate with Selectfluor afforded the desired 2-(fluoroalkyl)pyridine in good yield. Furthermore, 2-(fluoroalkyl)pyridines were obtained in good yields by saponification of methyl lithium 2-pyridylacetates and subsequent decarboxylative fluorination of lithium 2-pyridylacetates using the one-pot method. This reaction replaced the ester group with fluoride in a single step. Furthermore, this fluorination could be applied to the trifluoromethylthiolation reaction. The trifluoromethylthio group is strongly electron-withdrawing and highly lipophilic, and thus has attracted attention in the pharmaceutical sciences and related fields. Therefore, decarboxylative trifluoromethylthiolation was performed using the same method as the decarboxylative fluorination of 2-pyridylacetic acids with an electrophilic trifluoromethylthiolation reagent. The desired 2-(trifluoromethylthioalkyl)pyridine was obtained in good yield. Furthermore, we successfully performed the trifluoromethylthiolation as a one-pot reaction, analogous to the fluorination reactions.

Decarboxylative aldol reactions of tertiary carboxylic acids with trifluoropyruvate is described in chapter 4. As mentioned above, there are limited reports on the decarboxylative functionalization of tertiary β-oxocarboxylic acids in the absence of transition-metal catalysts. In contrast, our research

group reported that decarboxylative functionalization of tertiary β-ketocarboxylic acids proceeds smoothly in the presence of strongly electrophilic halogenating reagents. Based on this work, the decarboxylative aldol reaction using trifluoropyruvates, which are highly electrophilic aldol acceptors, proceeded smoothly with high diastereoselectivity. The desired aldol adducts were obtained in good yields with moderate-to-good enantioselectivity when the reactions were carried out using cinchonine, which is a chiral amine catalyst.

The decarboxylative fluorination of allyl-β-keto carboxylates with palladium catalyst is described in chapter 5. Decarboxylative allylic alkylation of allyl-β-keto carboxylates has been studied intensively since it was reported by the research group of J. Tsuji and T. Saegusa in 1980. However, there are very few reports on the decarboxylative functionalization of allyl-β-keto carboxylates with transition-metal catalysts, except for decarboxylative allylic alkylation. Based on this information, the decarboxylative fluorination of allyl-β-keto carboxylates using transition-metal catalysts were studied. Under optimized reaction conditions, the yield of the desired α-fluoroketone considerably improved when EtOH and BINAP were used as the solvent and ligand, respectively. However, the reaction was not enantioselective, even with chiral ligands.

Finally, the derivatization of chiral spiro compounds is described in chapter 6. In our previous work, we have reported that hydroxylation, thiolation, and azidation of tertiary α-chloroketones occurs via an $S_N2$ reaction. Furthermore, spirocyclic compounds were obtained in good yields via $S_N2$ pathway by using an α-chloroketone having a nucleophile at the end of the side chain. Therefore, the derivatization of the obtained spirocyclic compounds was proposed. The allyl alcohol analogues were first synthesized by the 1,2-reduction of the spirocyclic compounds using DIBAL-H. Etherification, Friedel-Crafts reaction, and hydrogenation over Pt/C of the obtained allyl alcohol analogs proceeded smoothly and the desired derivatized compounds were obtained with high diastereoselectivities and good yields.