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# Selective Hydrogenation and Transfer Hydrogenation for Post-Functional Synthesis of Trifluoromethylphenyl Diazirine Derivatives for Photoaffinity Labeling

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Additional information is available at the end of the chapter

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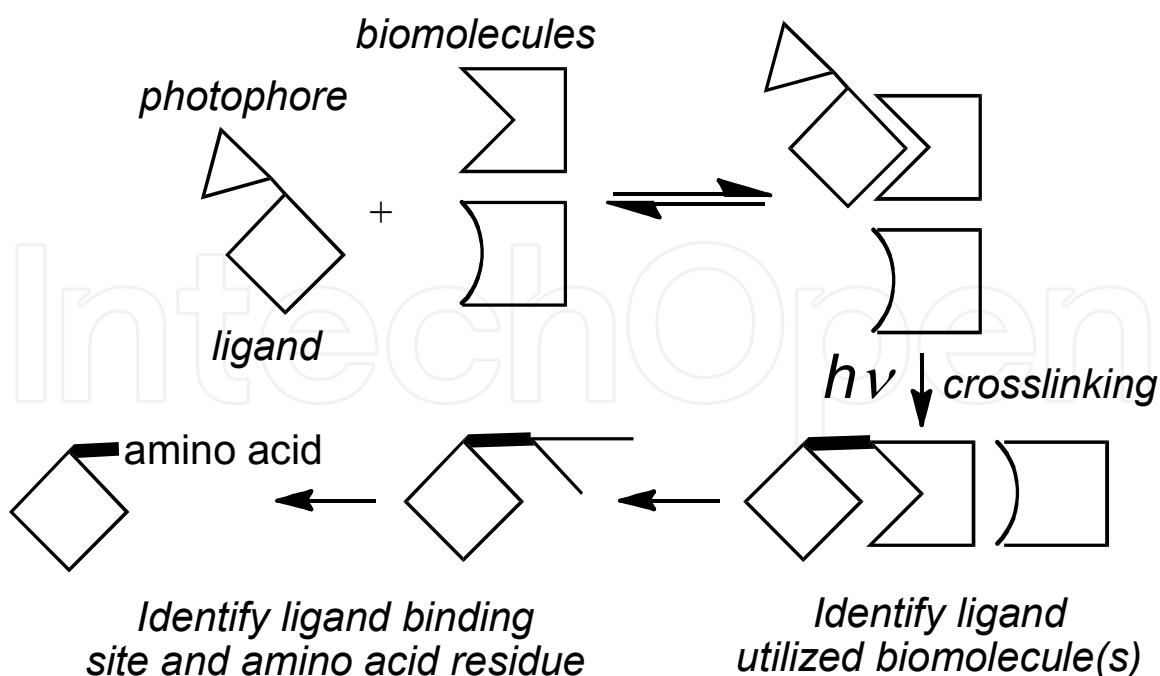
## 1. Introduction

### 1.1. Photoaffinity labeling

Elucidation of protein functions on the basis of structure–activity relationships can reveal the mechanisms of homeostasis functions in life and is one of the greatest interests of scientists. In the human body, many proteins are activated and/or inactivated by ligands to maintain homeostasis. Understanding the mechanism of molecular interactions between small bioactive ligands and proteins is an important step in rational drug design and discovery.

Photoaffinity labeling, which is one of the most familiar approaches for chemical biology analysis, was initiated using diazocarbonyl derivatives in 1962 (Singh et al., 1962). Many researchers have subsequently tried to establish alternative approaches for the direct identification of target proteins for the bioactive small ligands. These approaches are based on the affinity between the ligand and the target protein (*Figure 1*). Several reviews are published for the recent applications of photoaffinity labeling (Tomohiro et al., 2005; Hashimoto & Hatanaka, 2008).

To archive photoaffinity labeling, researchers have to prepare photoaffinity labeling ligands. The native ligands must be modified by photoreactive compounds (photophores) by organic synthesis.



**Figure 1.** Schematic representation of photoaffinity labeling

## 1.2. Photophore synthesis and their properties

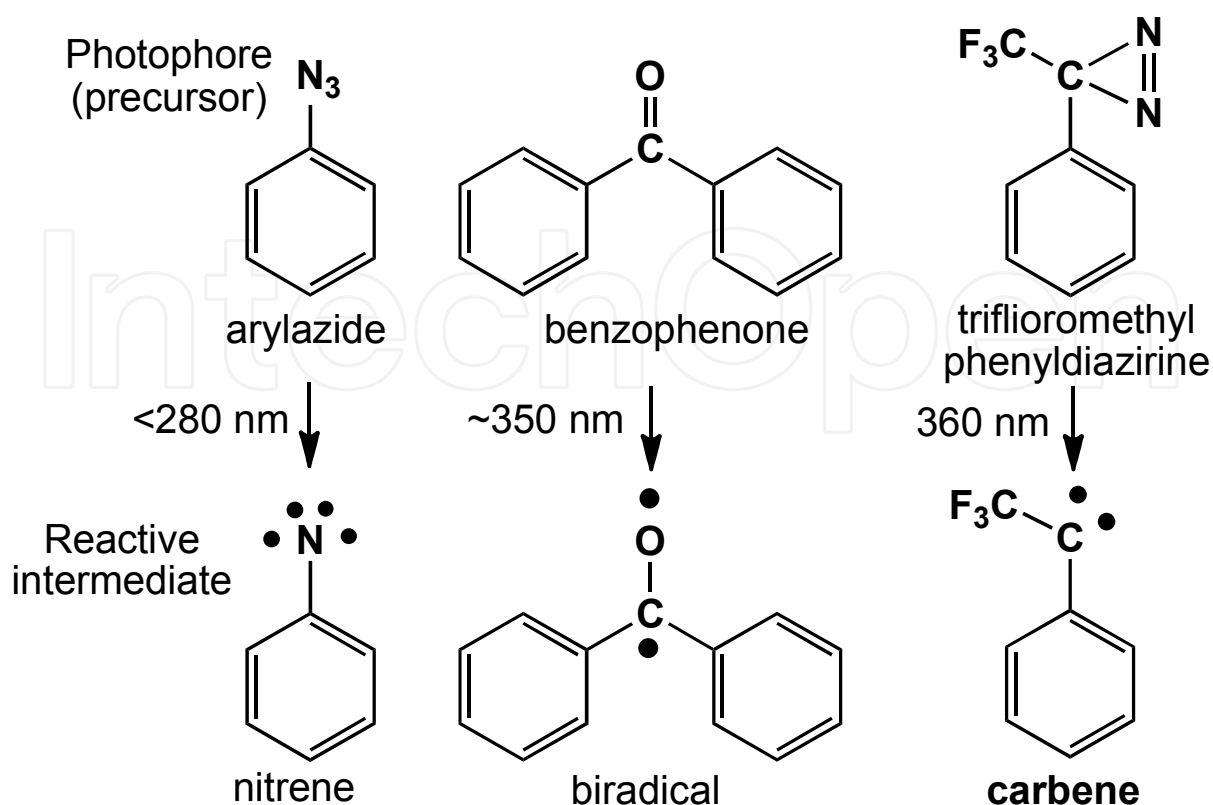
### 1.2.1. Selections of photophores

It is important which photophores are used for effective photoaffinity labeling (Figure 2). Typically, aryl azide, benzophenone, or trifluoromethylphenyldiazirine (TPD) have been used.

Aryl azides are photoactivated below a wavelength of 300 nm, which sometimes causes damage to biomolecules. In addition, these generate nitrenes (Platz, 1995) as active species and these sometimes rearrange to ketimines as undesired side products (Karney & Borden, 1997).

Benzophenones are photoreactivated with light over 350 nm and generate reactive triplet carbonyl states (Galardy et al., 1973). These regenerate ground-state carbonyl compounds and so benzophenone ligands are reusable for other photolabeling experiments, although the photophores sometimes need long photoirradiation times for labeling.

TPD, with a three membered ring and nitrogen-nitrogen double bond, are also photoreactivated with light over 350 nm. These generate carbenes, which are more highly reactive species than other photophores, and rapidly form cross-links to biomolecules with short photoirradiation times (Smith & Knowles, 1973). It has been reported that the photolysis of diazirines can cause diazo isomerization, giving undesired intermediates in photoaffinity labeling. Diazo isomerization can be suppressed by introduction of a trifluoromethyl group into a diazirinyl three-membered ring (Brunner et al., 1980; Nassal, 1983).



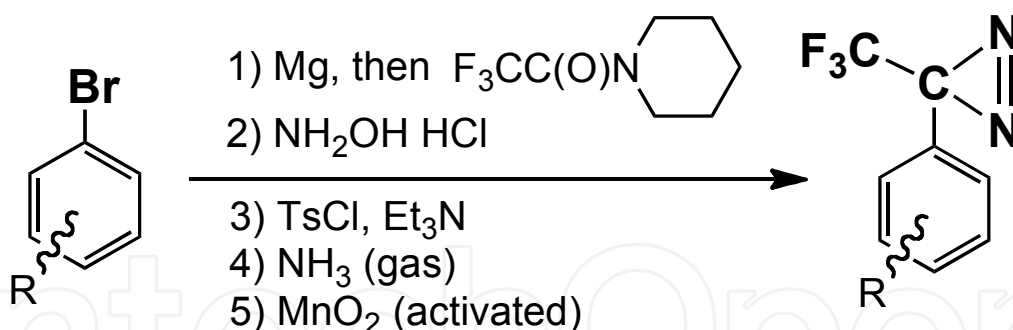
**Figure 2.** Photophores and their reactive intermediates following irradiation

Comparative irradiation studies of these three photophore types in living cells suggested that the irradiation needed for the generation of active species from azide and benzophenone caused cell death because long irradiation times are needed to incorporate the photophores into cell membrane surface biomolecules. By contrast, a carbene precursor – trifluoromethylphenyldiazirine (TPD) – did not cause cell death in the generation of active species (Hashimoto et al., 2001). Never-the-less, benzophenones (such as those attached to  $\gamma$ -secretase) are sometimes preferred for photoaffinity labeling experiments in vitro (Fuwa et al., 2006 & 2007).

### 1.2.2. Synthesis of trifluoromethylphenyldiazirine (TPD)

There are more several steps involved in the the constructions of the TPD skeleton than are needed for synthesis of other photophores. Synthesis of the TPD three-membered ring required at least five steps from the corresponding aryl halide derivatives (Figure 3).

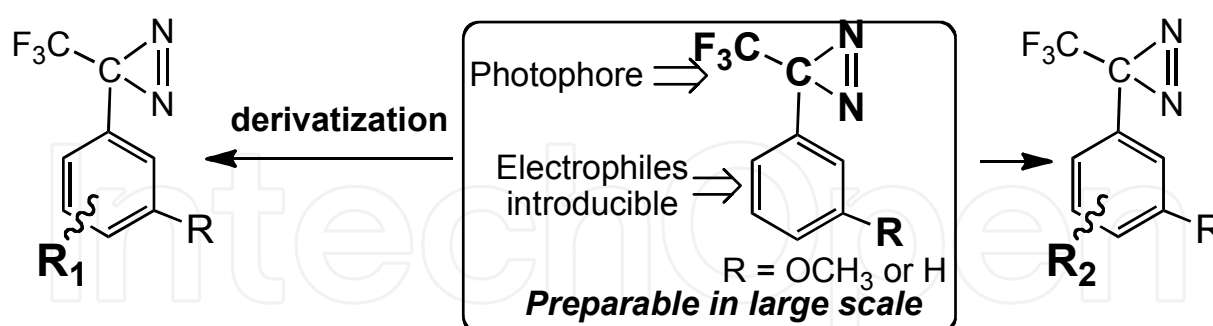
Although TPD is commercially available many are very expensive (1200 USD/0.5g for the simple TPD). In many previous synthetic routes the functional groups, which can be connected to ligands, tags and isotopes, should be pre-installed onto the benzene ring before constructions of three membered rings. The repeated construction of a diazirine moiety for each derivative is a drawback for application of the photophore for photoaffinity labeling.



**Figure 3.** Synthesis of trifluoromethylphenyldiazirine derivatives

### 1.2.3. Post-functional synthesis of TPD derivatives

Our breakthrough work on “post-functional” adaptation of diazirinyl compounds (Hatanaka et al., 1994, a & b) revealed that the trifluoromethyl-substituted three-membered ring was stable under many organic reaction conditions. Although the 3-(trifluoromethyl)diazirinyl moiety is categorized as an alkyl substituent, polarization means that the quaternary carbon atom is slightly positively charged, so the moiety is less activated towards electrophilic aromatic substitution than its unsubstituted counterpart (Hashimoto et al., 2006). We first selected the *m*-methoxy-substituted TPD (Fig. 4  $\text{R} = \text{OCH}_3$ ) as the mother skeleton, because: 1) the methoxy group strongly activates for electrophilic aromatic substitution, 2) the orientation of the substitution favors the *o*-position against the methoxy group, because the *p*-position is sterically hindered by the 3-(trifluoromethyl)diazirinyl moiety, and 3) demethylation of *m*-methoxy-TPD was easier than for *p*-methoxy-TPD, and realkylation of phenol derivative after demethylation was utilized for introduction of the tag.



**Figure 4.** Post-functional synthesis of trifluoromethylphenyldiazirine derivatives

It is somewhat difficult to derivatize unsubstituted TPD (Fig. 4,  $\text{R}=\text{H}$ ) as this is less susceptible to aromatic substitution than *m*-methoxy TPD. It would need harsh conditions for the substitutions on aromatic ring. For example, the formylation with dichloromethyl methyl ether was performed using titanium chloride in dichloromethane for the 3-methoxy diazirine at  $0^\circ\text{C}$  while the unsubstituted TPD did not afford formyl derivatives under the same condition. It is only archived when the trifluoromethanesulfonic acid, which is stronger acid than titanium chloride, was used as promoter for the reaction. These

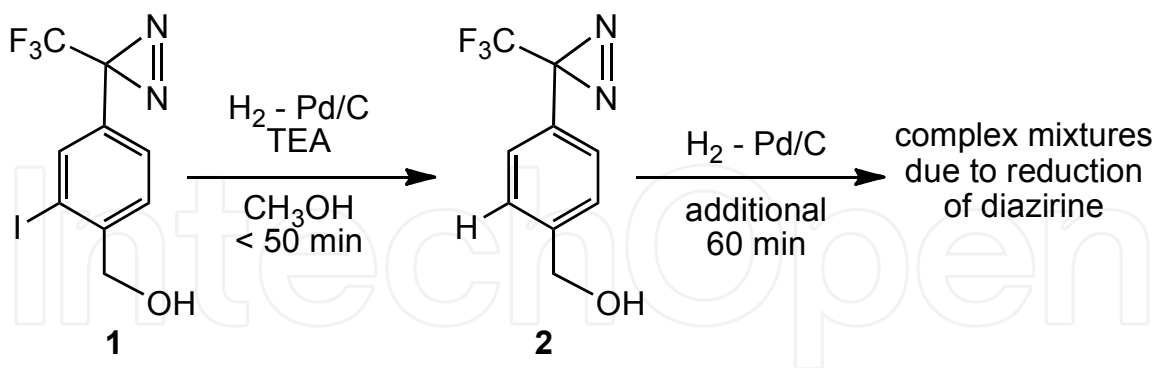
considerations directed our synthesis strategies towards derivatizations on the benzene ring after constructions of the trifluoromethyl diazirinyl ring (post-functional derivatizations). During the course of the studies, applications of hydrogenations to the TPD derivatives for post-functional synthesis are very important in associated derivatizations. However, the diazirinyl group consists of a nitrogen-nitrogen double bond in the structure and could be easily hydrogenated under the certain conditions. In this chapter, we would like to present a comprehensive summary for the hydrogenations that are compatible with or incompatible with the reaction conditions used for the trifluoromethylphenyl diazirinyl derivative. These considerations lead to effective post-functional derivatization approaches.

## 2. Selective hydrogenation methods over diazirinyl moiety for post-functional synthesis of TPD derivatives

### 2.1. Selective hydrogenation of carbon-iodine bond to carbon-hydrogen bond with H<sub>2</sub>-Pd/C

It has been reported that hydrogenation of diazirinyl compounds under H<sub>2</sub>-Pd/C at atmospheric pressure caused diazirinyl moiety reduction to diaziridine and further reduction of diaziridine moiety over a long time of treatment. Ambroise et al. found that hydrogenations of carbon-iodine bond in iodoarene are chemoselective.

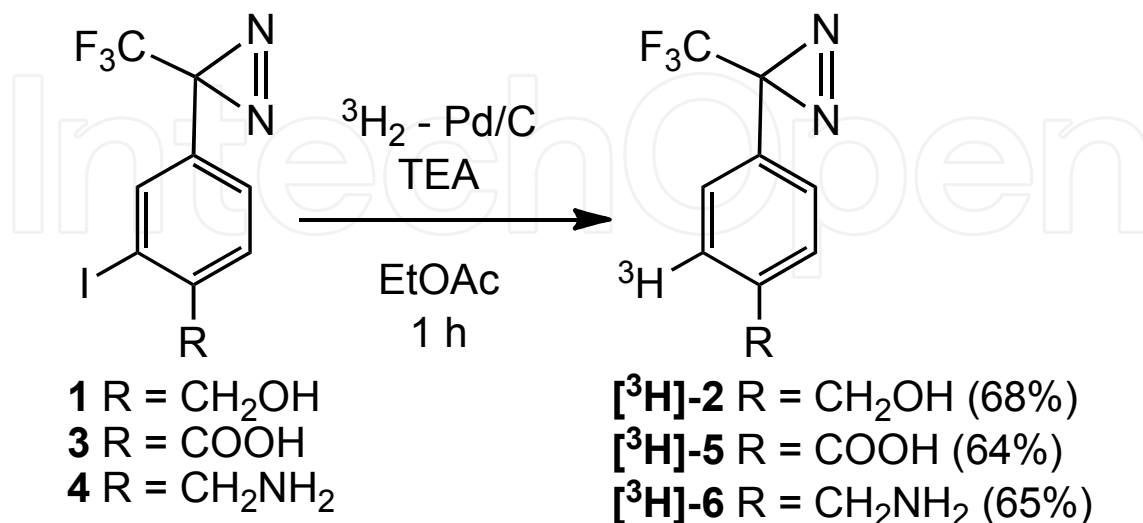
This occurs selectively over other easily reducible functional groups using Pd/C (10 mol%) under a hydrogen atmosphere, in the presence of triethylamine and within an hour (Ambroise et al., 2000). The selective hydrogenations can be applied for TPD derivatives. The iodoarene TPD derivative (**1**) was subjected to hydrogenation under the H<sub>2</sub>-Pd/C condition at atmospheric pressure (Fig.5).



**Figure 5.** Selective hydrogenation of iodoarene TPD derivatives (**1**). Selectivity for carbon-iodine bond to carbon-hydrogen bonds (**2**) occurs on Pd/C under a hydrogen atmosphere

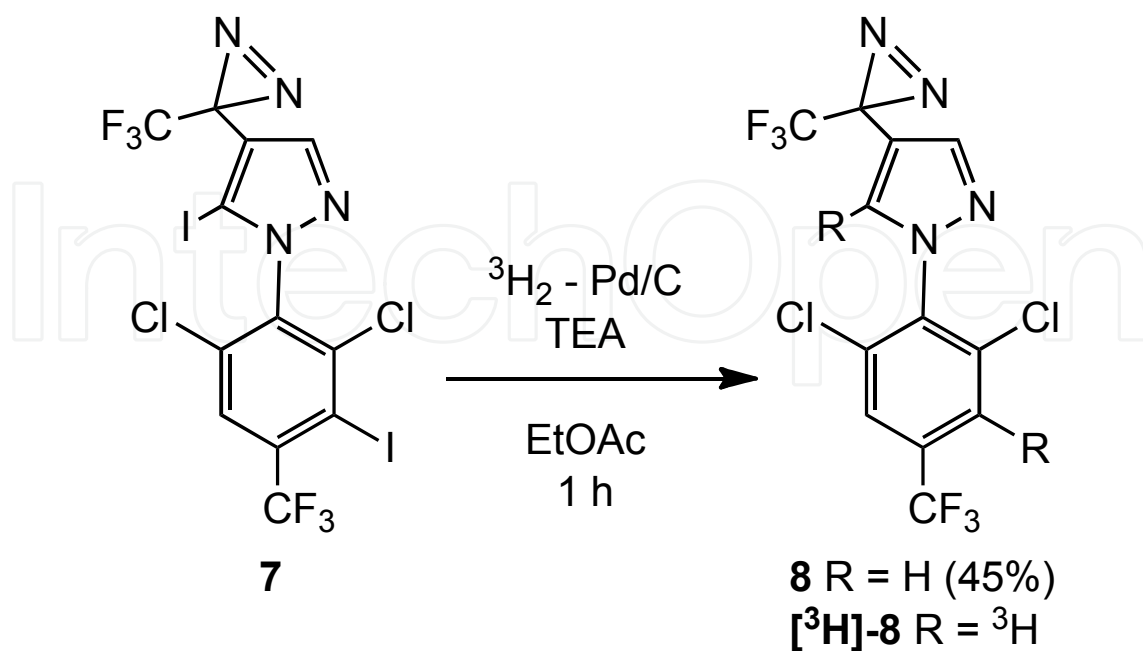
Detailed analysis revealed that the hydrogenation of carbon-iodine bond proceeded in parallel to the consumption of the starting material for 50 min. The hydrodeiodinated product (**2**) was subjected to further hydrogenolysis at the diazirinyl nitrogen-nitrogen double bond and compound **2** was completely consumed within an additional hour of hydrogenation. The chemoselective hydrogenation was applied to the synthesis of radiolabeled tritium TPD compounds from the corresponding iodoarene derivatives

(Ambroise et al., 2001) (Fig. 6). The synthesis of compounds with isotope incorporation has also been studied with other photophores including phenylazides and benzophenones (Faucher et al., 2002).



**Figure 6.** Selective tritiations of iodoarene TPD derivatives (**1**, **3** and **4**) for carbon-iodine bond to carbon-tritium bond on Pd/C under tritium atmosphere. Parentheses are isolated yields.

Sammelsson et al. performed selective hydrogenation for iodoarene derivative (**7**) over the chloroarene and trifluoromethyl diazirinyl group in the synthesis of photoreactive fipronil (**8**) using Pd/C under a H<sub>2</sub> or <sup>3</sup>H<sub>2</sub> atmosphere. The resulting compound was a high-affinity probe for GABA receptor (Sammelsson and Casida, 2003) (Fig. 7).

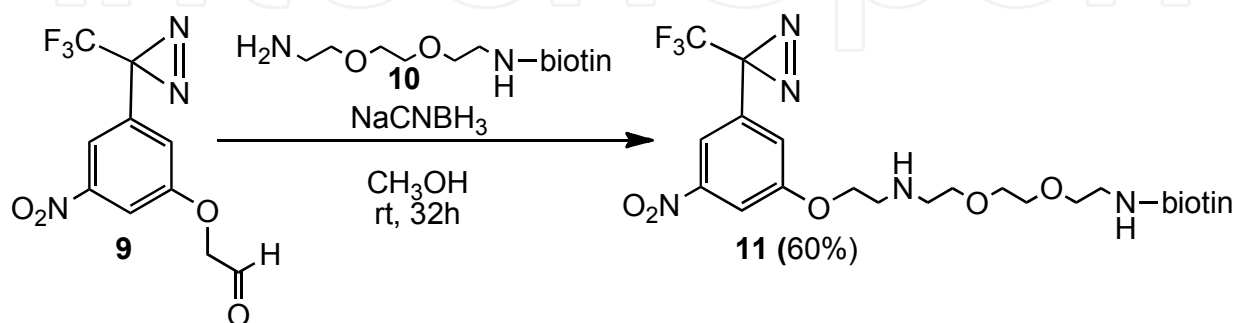


**Figure 7.** Selective hydrogenation or tritiations of carbon-iodine bond over carbon-chlorine bond and trifluoromethyl diazirinyl group of **7** with Pd/C under hydrogen or tritium atmosphere.



## 2.2. Selective hydrogenation of carbon-nitrogen double bonds (imines, Schiff's bases, reductive amination)

Imine (Schiff's base) TPD derivatives have been readily prepared from aldehyde (**9**) and primary amine (**10**). Catalytic hydrogenations of imines with H<sub>2</sub>-Pd/C were potentially available to afford amines, but side reactions at the nitrogen-nitrogen double bond on TPD derivatives prevented use of these catalytic hydrogenations. Hydride reductions for imines are acceptable for TPD derivatives and sodium cyanoborohydride has been used for the reductive amination leading to (**11**) (Fig. 8) (Daghighi et al., 2002).

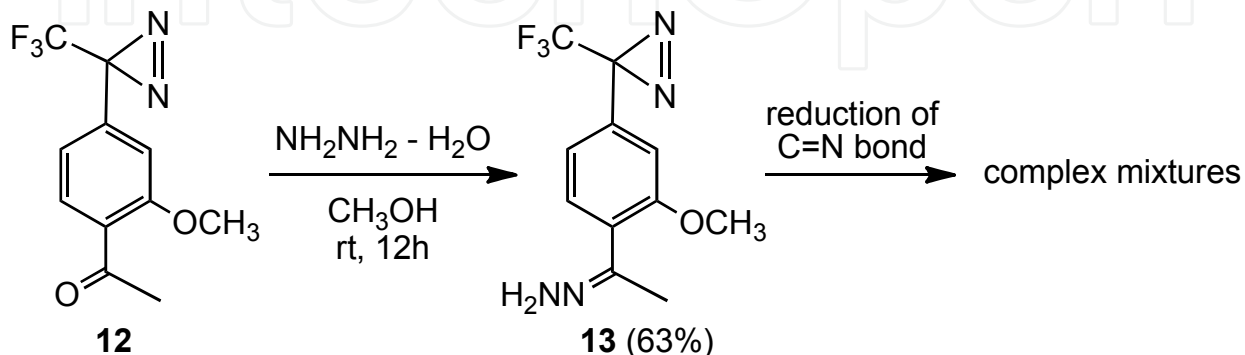


**Figure 8.** Reductive amination of TPD derivative (**9**) with biotin derivative (**10**)

Although this type of reaction is distinct from hydrogenation, we would like to briefly summarize reductions with hydride for use in TPD derivatization. NaBH<sub>4</sub> or LiAlH<sub>4</sub>, which were most common hydride sources, were compatible for TPD derivative chemistry that involved reduction of carbonyl groups. However those reduction reagents that incorporated a cofactor (ie CoCl<sub>2</sub>, NiCl<sub>2</sub> etc) promoted destruction of the diazirinyl ring (Hashimoto, unpublished results).

Many other hydride sources were compatible with TPD derivatizations.

Hydrazone derivatives of TPD (**13**) have been prepared with moderate yield from the corresponding TPD acetophenone (**12**) using hydrazine hydrate (1.5 eq). In early stages the acetophenone moieties were more reactive for the nucleophilic substitution with hydrazine hydrate than the reaction involving reduction of the diazirinyl group to diaziridines.



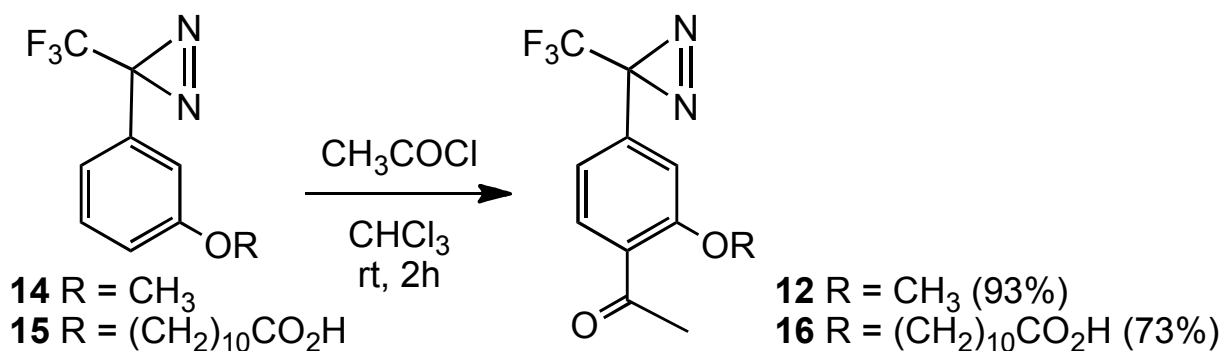
**Figure 9.** Selective TPD hydrazone formation (**13**) from acetophenone derivative (**12**)



The selective reduction of the carbon-nitrogen double bond in hydrazone to form carbon-nitrogen single bond was not achieved under various conditions (alcoholic KOH with reflux, *t*-BuOK-DMSO at room temperature, or *t*-BuOK-toluene with reflux). Instead the side reaction involving loss of the diazirinyl group occurred (Hashimoto, unpublished results). (Fig. 9)

### 2.3. Selective hydrogenation of carbon-oxygen double bonds (carbonyl and carboxyl) for the TPD derivatives.

Many methods for the reduction of carbon-oxygen double bonds have been reported. The carbonyl groups, which can be introduced by Friedel-Crafts acylation, are one of the most important synthetic methods for the post-functional synthesis. Friedel-Crafts reactions of TPD derivatives are not attainable because the trifluoromethyldiaziriny moiety has slight electron withdrawing properties (due to polarity of the quaternary carbon, which is connected directly to benzene ring). Furthermore the diazirinyl moiety was not stable over 25 °C in the presence of Lewis acids, which are the conditions generally used for catalysis in Friedel-Crafts reaction (Moss et al., 2001). TPD derivatives (**14** and **15**) can react at room temperature with the reactive acyl donor acetyl chloride when using aluminum chloride to introduce acetyl moiety (**12** and **16**) (Hashimoto et al., 2003, 2004) (Fig. 10).



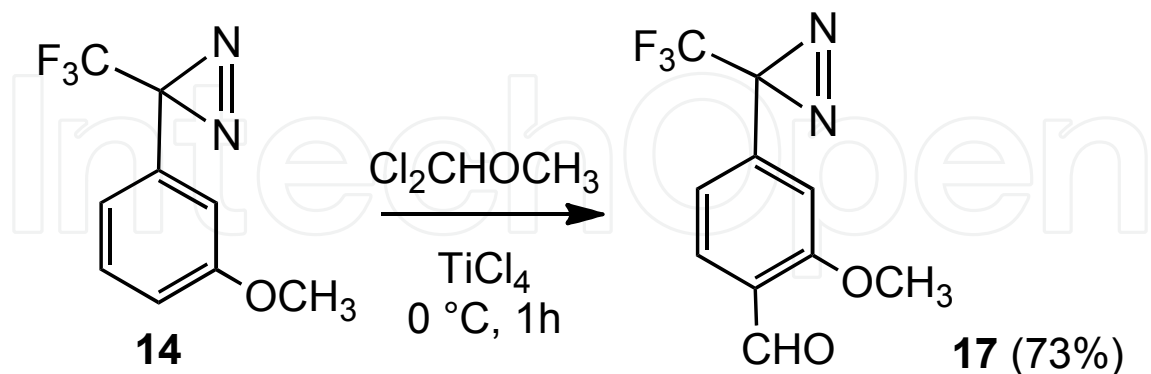
**Figure 10.** Friedel-Crafts acylation of TPD derivatives (**14** and **15**) with acetyl chloride and aluminum chloride.

On the other hand incorporation of less active acyl donors such as dichloromethyl methyl ether has to use stronger the Lewis acid, TiCl<sub>4</sub>. These conditions allow reaction with compound **14** to proceed (Hashimoto et al. 1997). Dichloromethane was used as solvent in early synthesis of this type but dichloromethyl methyl ether can also be used as solvent. This has enabled improvement in the yield of compound **17**. (Fig. 11)

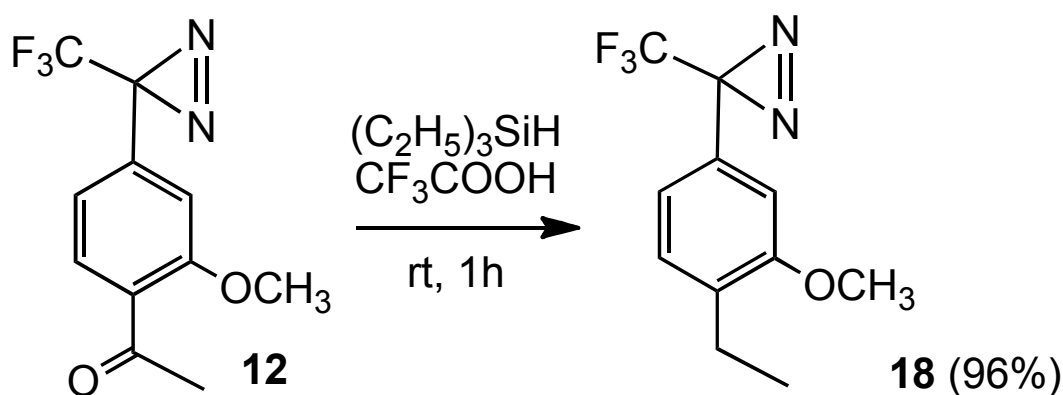
Hydrogenation of the Friedel-Crafts acylated products has been studied. Clemmensen reduction, Wolff-Kishner reduction and catalytic hydrogenation with Pd/C cannot be applied to synthesis of TPD derivative as these conditions lead to breakage of the diazirinyl moiety.

During the course of these trial screening reactions, it was found that transfer hydrogenation with triethylsilane in trifluoroacetic acid could be applied to TPD derivatives (**12**). The

conversions from benzyl carbonyl to methylene are very smooth and afforded the product (**18**) in very high yield without breaking the diazirinyl ring. (Fig. 12) (Hashimoto et al. 2003 & 2004)



**Figure 11.** Synthesis of benzaldehyde TPD derivative (**17**) with Friedel-Crafts alkylation, followed by hydrolysis from m-methoxy TPD (**14**)



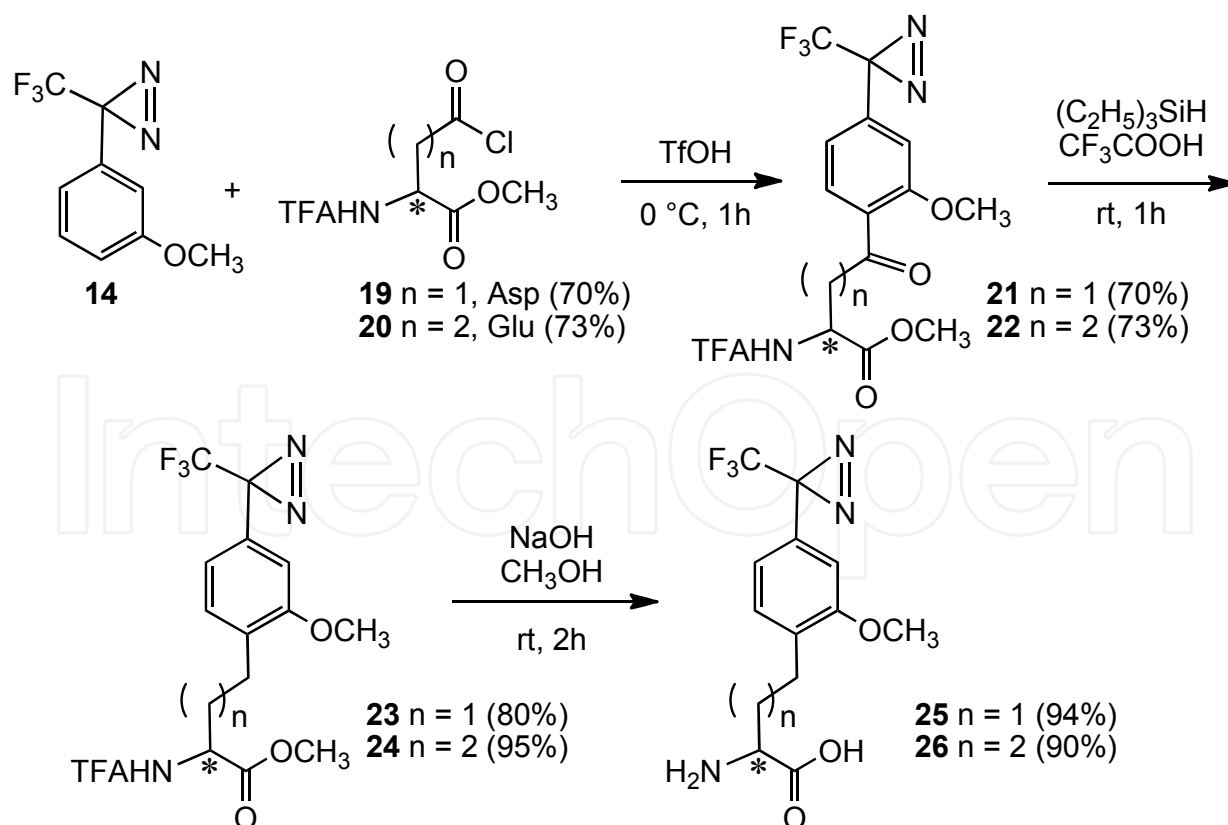
**Figure 12.** Transfer hydrogenation of TPD acetophenone derivative (**12**) with triethylsilane and trifluoroacetic acid

A sequence of reactions involving Friedel-Crafts acylation followed by reduction of the benzyl carbonyl to methylene enables us to stereocontrol synthesis of trifluoromethyldiazirinyl homo- and bishomo- phenylalanine derivatives. Synthesis of homo-phenylalanine has been reported using various methodologies including enzymatic methods (Zhao et al., 2002), Suzuki-coupling (Barfoot, et al., 2005), diastereoselective Michel addition (Yamada et al., 1998) and catalytic asymmetric hydrogenation (Xie, et al., 2000). These methods require the preparation of special reagents or precursors for the asymmetric synthesis of both enantiomers, especially aromatic compounds. Therefore one has to spend time and effort on establishment of TPD derivatizations without decomposition of diazine.

Amino acids are one of the most popular precursors and easily available compounds for stereo controlled synthesis using the asymmetric center. Friedel-Crafts reactions between

aromatics and a side chain of aspartic acid (Asp) or glutamic acid (Glu) are some of the key reactions for asymmetric synthesis for both homo- or bishomo- phenylalanine enantiomers' skeletons. (Reifenrath, et al. 1976; Nordlander et al., 1985; Melillo et al., 1987; Griesbeck & Heckroth, 1997; Xu et al., 2000; Lin et al., 2001)

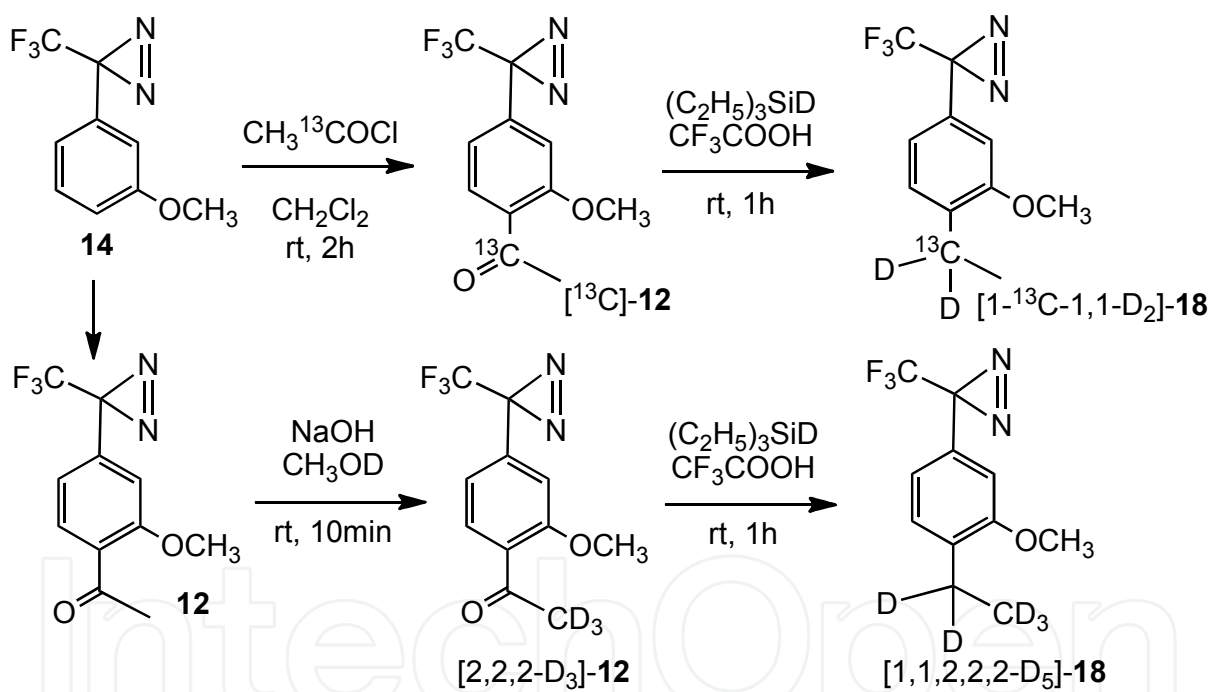
It has been reported that synthesis of homophenylalanine using a Friedel-Crafts reaction of Asp anhydride (*N*-unprotected or *N*-protected) with  $\text{AlCl}_3$  requires use of large excesses of aromatics and reflux in organic solvent for long durations (Xie, et al., 2000). These synthesis conditions cannot apply the equivalent condition of amino acid and TPD derivatives. Furthermore, the diazirinyl ring did not tolerate heating in the presence of Lewis acids. After Friedel-Crafts acylation, the constructed benzyl carbonyl group was hydrogenated to methylene under  $\text{H}_2$ -Pd/C, which is not suitable for TPD derivatives. These difficulties were overcome Friedel-Crafts acylation of TPD derivative (**14**) and side chain derivatives of Asp (**19**) or Glu (**20**) using trifluoromethanesulfonic acid followed by ionic hydrogenation of benzylcarbonyl group to methylene with triethylsilane - trifluoroacetic acid. After constructions of the homo- (**23**) or bishomo- (**24**) phenylalanine skeletons, removal of the protective groups afforded TPD containing homo- (**25**) or bishomo- (**26**) phenylalanine while maintaining the stereochemistry of starting Asp or Glu (Murai et al., 2009; Murashige et al. 2009) (Fig. 13).



**Figure 13.** Stereo controlled synthesis of homo- (**25**) and bishomo- (**26**) phenylalanine TPD derivatives from *m*-methoxy TPD (**14**) and optically pure Asp (**19**) or Glu (**20**) derivatives

### 2.3.1. Selective hydrogenation of carbon-oxygen double bonds with stable isotope labeling

Established methods for the post-functional synthesis (described in the previous section) have facilitated the preparation of stable isotope labeled TPD. Stable isotopes act as a tag for the exogenous ligand derivatives on mass spectrometry. The methodologies will be very useful for the field of photoaffinity labeling to detect the labeled components. Friedel-Crafts acylation with 1-<sup>13</sup>C acetyl chloride, which is a relatively inexpensive reagent compared with other <sup>13</sup>C labeled compounds, afforded <sup>13</sup>C labeled acetophenone derivative ([<sup>13</sup>C]-**12**) in moderate yield. Hydrogenations by deuterium atom of the acetophenone has been applied using various conditions. Deuterium was effectively introduced to the methylene moiety by deuterium labeled triethylsilane (Et<sub>3</sub>SiD) and unlabeled trifluoroacetic acid (CF<sub>3</sub>COOH) to afford [1-<sup>13</sup>C-1, 1-D<sub>2</sub>]-**18**. It is not necessary to use deuterium labeled trifluoroacetic acid for the deuteration. (Hashimoto & Hatanaka, 2004)



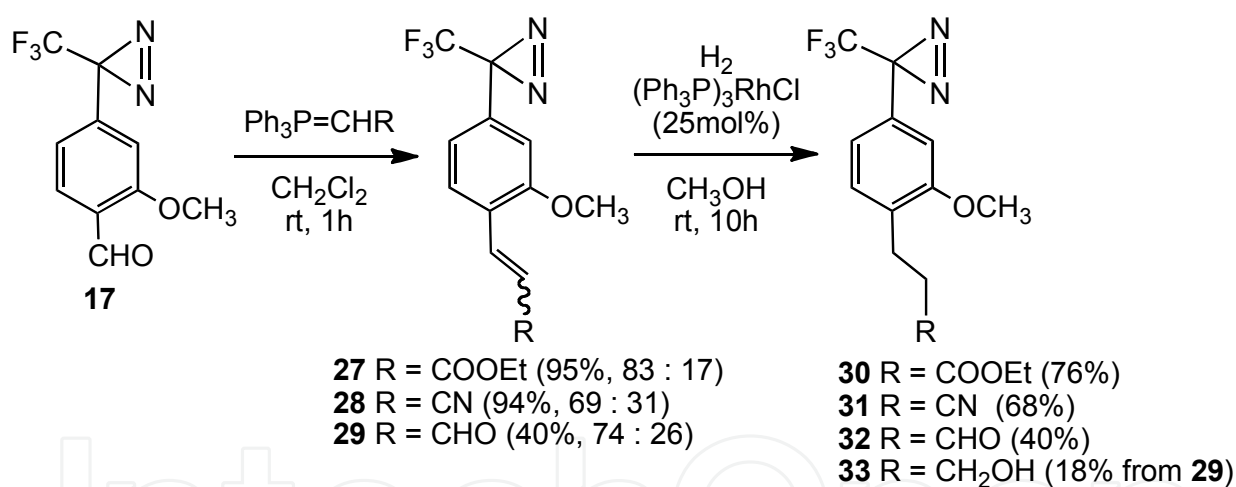
**Figure 14.** Synthesis of stable isotope labeled TPD derivatives with transfer hydrogenation

The  $\alpha$ -position of the carbonyl groups was susceptible to very fast hydrogen-deuterium exchange using sodium hydroxide (NaOH) and methanol-OD (CH<sub>3</sub>OD) at room temperature. There are no serious decrements of deuterium incorporation with various work up to synthesis [2,2,2-D<sub>3</sub>]-**12**. After that, ionic hydrogenation with Et<sub>3</sub>SiD and trifluoroacetic acid afforded 5 deuterium incorporated TPD derivatives ([1,1,2,2,2-D<sub>5</sub>]-**18**). (Fig. 14). These synthetic methodologies have also been applied to synthesis of deuterium incorporated photoreactive fatty acid derivatives. (Murai et al. 2010)

## 2.4. Selective hydrogenation of carbon-carbon double bonds for the TPD derivatives

The synthetic strategies for the Wittig reaction, followed by hydrogenation are amongst the major methods for carbon elongation derivatizations. These synthetic methods have not been compatible with synthesis of the TPD derivatives. This is because conditions for establishment for the selective hydrogenation (reduction) for the carbon-carbon double bond over that for nitrogen-nitrogen double bond on TPD are not easily achieved.

We found Wilkinson's catalyst, chlorotris(triphenylphosphine)rhodium(I) in methanol has specificity for the target reaction. The alkene containing TPD derivatives (**27-29**), which are synthesized from Wittig reaction for TPD aldehyde (**17**) and stable ylides, were subjected to hydrogenation with H<sub>2</sub>-Wilkinson's catalyst at atmospheric pressure. It was observed that 25mol% of Wilkinson's catalyst required for complete hydrogenation. The  $\alpha$ ,  $\beta$ -unsaturated ester (**27**), nitrile (**28**) and aldehyde (**29**) were also hydrogenated under these conditions. The aldehyde carbonyl group conversion to primary alcohol (**33**) was only partially complete. (Fig. 15)



**Figure 15.** Synthesis of  $\alpha$ ,  $\beta$ -unsaturated carbonyl TPD derivatives and their hydrogenation with Wilkinson's catalyst

The hydrogenation of **27** and **28** with deuterium gas allowed effective incorporation of the deuterium atom into these compounds (Hashimoto et al., 2007).

## 3. Conclusions

Hydrogenations are very important for post-functional synthesis of TPD compounds.

It is very important for synthesis of TPD compounds that a range of hydrogenation methods are investigated. Selective hydrogenations in the presence of nitrogen-nitrogen double

bonds in TPD have been established. Very strict conditions are necessary as the important nitrogen-nitrogen double bond can easily be lost. The establishments of a range of hydrogenation methods, together with the limitations of these methods that are described in this review, will facilitate further progress in the post-functional preparations of TPD. These chemical considerations could generate further widespread use of these biochemically ideal photoaffinity labels.

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## 4. References

- Ambroise, Y.; Mioskowski, C.; Djéga-Mariadassou, G. & Rousseau, B. (2000). Consequences of affinity in heterogeneous catalytic reactions: highly chemoselective hydrogenolysis of iodoarenes. *J. Org. Chem.* 65, 7183-7186.
- Barfoot, C. W.; Harvey, J. E.; Kenworthy, M. N.; Kilburn, J. P.; Ahmed, M. & Taylor, R. J. K. (2005). Highly functionalised organolithium and organoboron reagents for the preparation of enantiomerically pure  $\alpha$ -amino acids. *Tetrahedron*, 61, 3403-3417.
- Brunner, J.; Senn, H. & Richards, F. M. (1980). 3-Trifluoromethyl-3-phenyldiazirine. A new carbene generating group for photolabeling reagents. *J. Biol. Chem.* 255, 3313-3318
- Daghish, M.; Hennig, L.; Findeisen, M.; Giesa, S., Schumer, F.; Hennig, H.; Beck-Sickinger, A. G. & Welzel, P. (2002) Tetrafunctional photoaffinity labels based on Nakanishi's *m*-nitroalkoxy-substituted phenyltrifluoromethyldiazirine. *Angew. Chem. Int. Ed.* 41, 2293-2297
- Faucher, N.; Ambroise, Y.; Cintrat, J. -C.; Doris, E.; Pillon, F. & Rousseau, B. (2002). Highly chemoselective hydrogenolysis of iodoarenes. *J. Org. Chem.* 67, 932-934.



- Fuwa, H.; Hiromoto, K.; Takahashi, Y.; Yokoshima, S.; Kan, T.; Fukuyama, T.; Iwatsubo, T.; Tomita, T. & Natsugari, H. (2006). Synthesis of biotinylated photoaffinity probes based on arylsulfonamide  $\gamma$ -secretase inhibitors, *Bioorg. Med. Chem. Lett.* 16, 4184–4189.
- Fuwa, H.; Takahashi, Y.; Konno, Y.; Watanabe, N.; Miyashita, H.; Sasaki, M.; Natsugari, H.; Kan, T.; Fukuyama, T.; Tomita, T. & Iwatsubo, T. (2007). Divergent synthesis of multifunctional molecular probes to elucidate the enzyme specificity of dipeptidic  $\gamma$ -secretase inhibitors. *ACS Chem. Biol.* 2, 408–418.
- Galardy, R. E.; Craig, L. C. & Printz, M. P. (1973). Benzophenone triplet: a new photochemical probe of biological ligand-receptor interactions. *Nat. New Biol.* 242, 127–128.
- Griesbeck, A. G. & Heckroth, H. (1997). A simple approach to  $\alpha$ -amino acids by acylation of arenes with *N*-acyl aspartic anhydrides. *Synlett* 11, 1243–1244.
- Hashimoto, M.; Kanaoka, Y. & Hatanaka, Y. (1997). A versatile approach for functionalization of 3-aryl-3-trifluoromethyl diazirine photophore. *Heterocycles*, 46, 119–123.
- Hashimoto, M.; Yang, J. & Holman, G. D. (2001). Cell-surface recognition of biotinylated membrane proteins requires very long spacer arms: An example from glucose-transporter probes. *CHEMBIOCHEM* 2, 52–59.
- Hashimoto, M.; Hatanaka, Y. & Nabeta, K. (2003). Effective synthesis of a carbon-linked diazirinyl fatty acid derivative via reduction of the carbonyl group to methylene with triethylsilane and trifluoroacetic acid. *Heterocycles* 59, 395–398.
- Hashimoto, M. & Hatanaka, Y. (2004). Simple synthesis of deuterium and  $^{13}\text{C}$  labeled trifluoromethyl phenyldiazirine derivatives as stable isotope tags for mass spectrometry. *Chem. Pharm. Bull.* 52, 1385–1386.
- Hashimoto, M.; Kato, Y. & Hatanaka, Y. (2006) Simple method for the introduction of iodo-label on (3-trifluoromethyl) phenyldiazirine for photoaffinity labeling. *Tetrahedron Lett.* 47, 3391–3394.
- Hashimoto, M.; Kato, Y. & Hatanaka, Y. (2007). Selective hydrogenation of alkene in (3-trifluoromethyl) phenyldiazirine photophore with Wilkinson's catalyst for photoaffinity labeling. *Chem. Pharm. Bull.* 55, 1540–1543.
- Hashimoto, M. & Hatanaka, Y. (2008). Recent progress in diazirine-based photoaffinity labeling. *Eur. J. Org. Chem.* 2513–2523
- Hatanaka, Y.; Hashimoto, M.; Kurihara, H.; Nakayama, H. & Kanaoka, Y. (1994a). A novel family of aromatic diazirines for photoaffinity labeling. *J. Org. Chem.* 59, 383–387.
- Hatanaka, Y.; Hashimoto, M.; Nakayama, H. & Kanaoka, Y. (1994b). Syntheses of nitro-substituted aryl diazirines. An entry to chromogenic carbene precursors for photoaffinity labeling. *Chem. Pharm. Bull.* 42, 826–831.
- Karney, W. L. & Borden, W. T. (1997). Why does *o*-fluorine substitution raise the barrier to ring expansion of phenylnitrene? *J. Am. Chem. Soc.* 119, 3347–3350.



- Lin, W.; He, Z.; Zhang, H.; Zhang, X.; Mi, A. & Jiang, Y. (2001). Amino acid anhydride hydrochlorides as acylating agents in Friedel-Crafts reaction: a practical synthesis of L-homophenylalanine. *Synthesis* 7, 1007-1009.
- Melillo, D. G.; Larsen, R. D.; Mathre, D. J.; Shukis, W. F.; Wood, A. W. & Colleluori, J. R. (1987). Practical enantioselective synthesis of a homotyrosine derivative and (R,R)-4-propyl-9-hydroxynaphthoxazine, a potent dopamine agonist. *J. Org. Chem.* 52, 5143-5150.
- Moss, R. A.; Fedé, J. -M. & Yan S. (2001). SbF<sub>5</sub>-mediated reactions of oxafuorodiazirines. *Org. Lett.* 3, 2305-2308.
- Murai, Y.; Hatanaka, Y.; Kanaoka, Y. & Hashimoto, M. (2009). Effective synthesis of optically active 3-phenyl-3-(3-trifluoromethyl) diazirinyl bishomophenylalanine derivatives, *Heterocycles* 79, 359-364.
- Murai, Y.; Takahashi, M.; Muto, Y.; Hatanaka, Y. & Hashimoto, M. (2010). Simple deuterium introduction at  $\alpha$ -position of carbonyl in diazirinyl derivatives for photoaffinity labeling. *Heterocycles*, 82, 909 - 915.
- Murashige, R.; Y. Murai, Y.; Hatanaka, Y. & Hashimoto, M. (2009). Effective synthesis of optically active trifluoromethyldiazirinyl homophenylalanine and aroylalanine derivatives with Friedel-Crafts reactions in triflic acid. *Biosci. Biotechnol. Biochem.* 73, 1377-1380.
- Nassal, M. (1983). 4-(1-Azi-2,2,2-trifluoroethyl)benzoic acid, a highly photolabile carbene generating label readily fixable to biochemical agents. *Liebigs Ann. Chem.* 1510- 1523.
- Nordlander, J. E.; Payne, M. J.; Njoroge, F. G.; Vishwanath, V. M.; Han, G. R.; Laikos, G. D. & Balk, M. A. (1985) A short enantiospecific synthesis of 2-amino-6,7-dihydroxy- 1,2,3,4-tetrahydronaphthalene (ADTN). *J. Org. Chem.* 1985, 50, 3619-3622.
- Platz, M. S. (1995). Comparison of phenylcarbene and phenylnitrene. *Acc. Chem. Res.* 28, 487-492.
- Reifenrath, W. G.; Bertelli, D. J.; Micklus M. J. & Fries, D. S. (1976). Stereochemistry of friedel-crafts addition of phthalylaspartic anhydride to benzene. *Tetrahedron Lett.* 17, 1959-1962.
- Sammelson, R. E. & Casida, J. E. (2003). Synthesis of a tritium-labeled, fipronil-based, highly potent, photoaffinity probe for the GABA receptor. *J. Org. Chem.* 68, 8075-8079.
- Singh, A.; Thornton, E. R. & Westheimer, F. H. (1962). The photolysis of diazoacetyl-chymotrypsin. *J. Biol. Chem.* 237, PC3006-PC3008.
- Smith, R. A. G. & Knowles, J. R. (1973). Aryldiazirines. potential reagents for photolabeling of biological receptor sites. *J. Am. Chem. Soc.* 95, 5072-5073.
- Tomohiro, T.; Hashimoto, M. & Hatanaka, Y. (2005). Cross-linking chemistry and biology: development of multifunctional photoaffinity probes. *Chemical Record*, 5, 385-395
- Yamada, M.; Nagashima, N.; Hasegawa, J. & Takahashi, S. (1998). A highly efficient asymmetric synthesis of methoxyhomophenylalanine using michael addition of phenethylamine. *Tetrahedron Lett.* 39, 9019-9022.

- Xie, Y.; Lou, R.; Li, Z.; Mi, A. & Jiang, Y. (2000). DPAMPP in catalytic asymmetric reactions: enantioselective synthesis of L-homophenylalanine. *Tetrahedron: Asymm.* 11, 1487-1494.
- Xu, Q.; Wang, G.; Wang, X.; Wu, T.; Pan, X.; Chan, A. S. C. & Yang, T. (2000). The synthesis of L-(+)-homophenylalanine hydrochloride. *Tetrahedron: Asymm.* 11, 2309-2314.
- Zhao, H.; Luo, R. G.; Wei, D. & Malhotra, S. V. (2002). Concise synthesis and enzymatic resolution of L-(+)-homophenylalanine hydrochloride, *Enantiomer*, 7, 1-3.

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