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光促二氟烯丙基化合物的*E*→*Z*异构化反应

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摘要 有机氟化物在材料、医药以及能源等领域, 有着广泛的应用前景. 其中, 二氟甲基(CF_2)作为羰基或醚键的生物电子等排体, 其引入能显著改变目标分子的生物活性. 目前发展的二氟烯丙基化合物都以得到热力学稳定的反式(*E*)构型为主. 本文建立了由易得的*E*-二氟烯丙基化合物异构为*Z*-二氟烯丙基化合物的方法. 该反应由2,4,5,6-四咔唑基-1,3-苯二腈(4CzIPN)催化的光化学反应实现, 反应温和、操作简便、经济性好, 为*Z*-二氟烯丙基化合物的大量制备建立了高效方法. 论文还通过克级反应和产物衍生化对当前反应的实用性进行了研究. 机理研究认为, 该反应经过三线态-三线态能量转移(TTET)过程完成.

关键词 光催化, 异构化, 二氟烯丙基, 4CzIPN

由于氟原子的特殊性质, 有机氟化物在医药、农药、材料、化工等领域, 扮演着极其重要的角色. 据统计, 全球20%~25%的医药和30%的农药分子中含有至少一个氟原子[1~7]. 在原子性质上, 氟原子具有高电负性和小原子半径, C–F(δ-)在结构上能够替代C–H(δ+), 实现局部电荷的反转[8]. 氟原子在药物化学中被认为是羟基官能团的生物电子等排体, 氟原子的引入能引起先导化合物溶解性、疏水性、代谢稳定性、生物利用度的显著改变. 在各种含氟基团中, 二氟烷基(CF_2)的引入对于药物分子尤其重要, 因其能够改变有机分子的基态构象、代谢稳定性, 提高生物利用度, 增加对靶器官的选择性, 降低药物的使用剂量[9~11]. 例如, 他氟前列素(ttafluprost)是一种前列腺素类似物, 作为局部用药被用于缓解青光眼和高眼压症[12]、格卡瑞韦(glecaprevir)是一种NS3/4A蛋白酶抑制剂被用于治疗丙型肝炎[13,14]、KAG-308是一种前列腺素E2受体亚型激动剂用于治疗溃疡性结肠炎[15](图1). 这些药物分子不仅是二氟烷基化合物, 而且都含有二氟烯丙基的关键结构.

除具有特殊生物活性外, 二氟烯丙基化合物也被用作合成其他含氟化合物的重要中间体, 通过环氧化、环加成、双羟化、氧化、芳基化、氢化等反应快速转化为其他类型的化合物[16~23]. 因此, 二氟烯丙基化合物的合成方法引起了合成化学工作者的广泛关注. 传统的过渡金属催化和近年来快速发展的光化学反应在二氟烯丙基化合物的合成中占有重要地位. 其中, 卤代二氟烷烃作为二氟烷基的重要来源, 炔烃和卤代二氟烷烃的自由基加成反应及原子转移加成反应(ATRA)具有较好的原子利用率, 成为了研究的热点[24~27](图2(a)). 活泼烯烃与卤代二氟烷烃的自由基偶联反应[28~32]也被用于二氟烯丙基化合物的合成. 然而, 目前发展的二氟烯丙基化合物的合成方法都以得到反式烯烃为主. 二氟烯丙基除了含有两个氟原子外, 其结构中的碳碳双键也对生物活性起到了重要作用. 含有顺式双键(*Z*)和反式双键(*E*)的烯烃不仅表现出不同的物理性质和化学

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Li Z, Yang C H, Zhao H Y, et al. Visible light promoted *E*→*Z* isomerization of difluoroallyl compounds (in Chinese). Chin Sci Bull, 2024, 69: 4763–4772, doi: 10.1360/TB-2024-0485

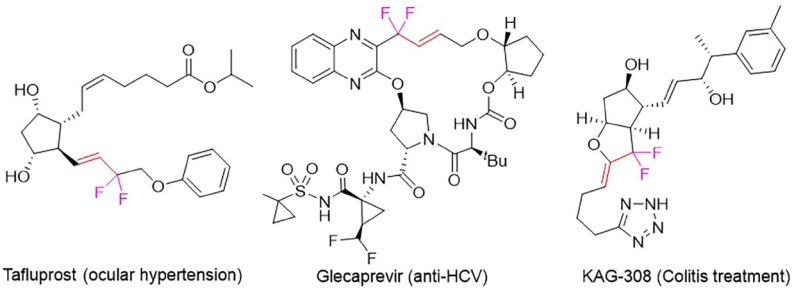


图 1 (网络版彩色)具有二氟烯丙基结构的生物活性分子
Figure 1 (Color online) Biologically active molecules with allylic difluoride moieties

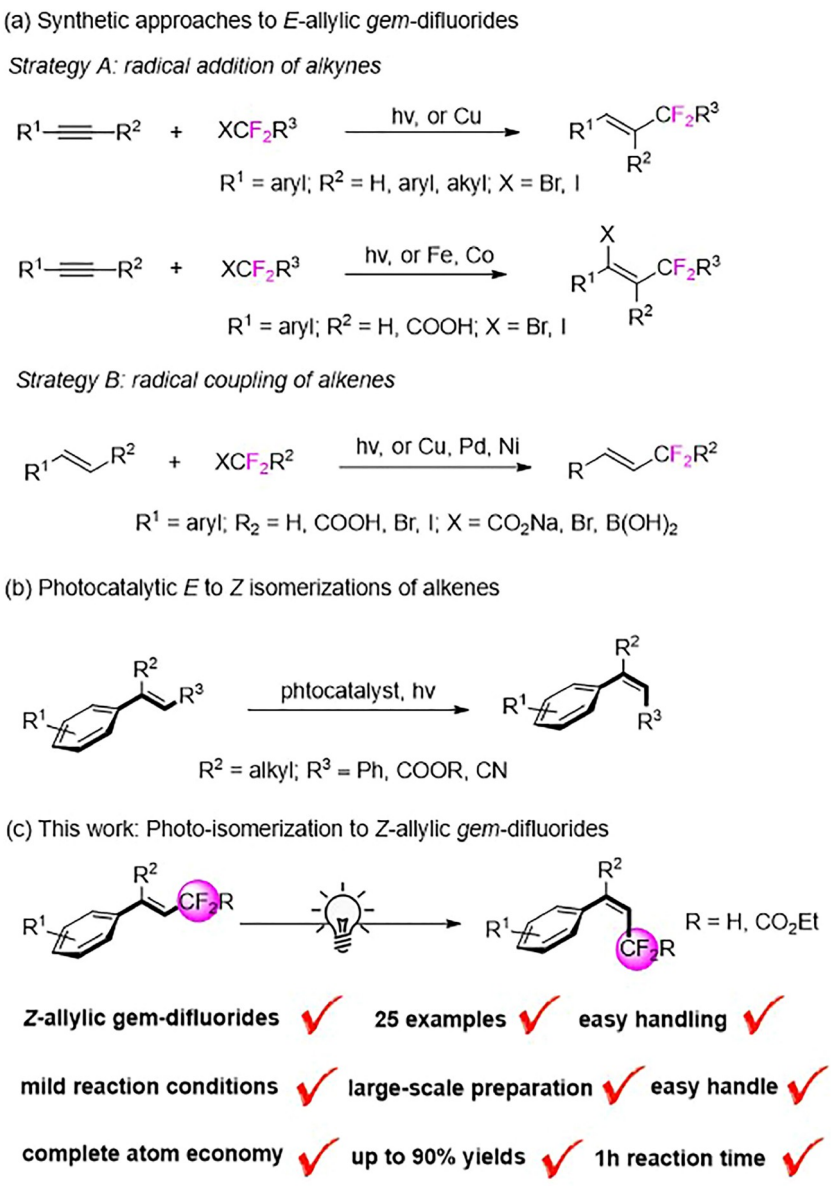


图 2 (网络版彩色)二氟烯丙基化合物的合成方法. (a) 反式二氟烯丙基化合物的合成方法. (b) 光促烯烃的顺式反式异构化. (c) 本文工作: 光促顺式氟烯丙基化合物的合成
Figure 2 (Color online) Synthetic methods for allylic *gem*-difluorides. (a) Synthetic approaches to *E*-allylic gem-difluorides. (b) Photocatalytic *E* to *Z* isomerizations of alkenes. (c) This work: Photo-isomerization to *Z*-allylic gem-difluorides

性质, 其生物活性也有显著区别. 例如, 含有反式双键的白藜芦醇比起顺式异构体生物活性突出[33]; 与顺式脂肪酸相比, 反式脂肪酸可能增加血液中的低密度脂蛋白胆固醇含量, 增加冠心病的风险[34]; 一种含有顺式单氟烯烃结构的Xa因子抑制剂, 相比反式表现出更优异的生物活性[35].

由于不同构型的烯烃混合物往往很难通过常规手段实现快速分离, 所以不同构型的烯烃的高选择性合成具有重大意义. 而烯烃的合成方法大多以得到具有更好的热力学稳定性的反式烯烃为主, 并且在加热条件下, 反式烯烃可以向顺式烯烃转化[36]. 因直接合成热力学不稳定的顺式烯烃具有较大挑战性, 由反式烯烃向顺式烯烃转化(*E*→*Z*)的异构化引起了重点关注. 烯烃的*E*→*Z*光促异构化反应具有100%的原子利用率, 近年来得到了蓬勃发展[37](图2(b)). 合成工作者先后开发出了二苯乙烯[38,39]、肉桂酸酯[40]、肉桂腈[41]、烯丙基胺[42]、烯基硼酸酯[43]、苯乙烯基溴[44]等化合物的光促*E*→*Z*异构化反应. 然而, 合成*Z*-烯丙基氟化物的异构化反应还未报道. 本课题组[26,45]在研究二氟烷基化合物合成方法的基础上, 利用有机光催化剂4CzIPN激发态的能量转移机制, 实现了反式二氟烯丙基化合物的有效活化, 选择性地得到了顺式二氟烯丙基化合物. 该转化方法无需金属催化剂, 操作便捷、条件温和、环境友好, 并且能够用于顺式二氟烯丙基化合物的大量制备(图2(c)).

1 实验

1.1 试剂与仪器

核磁共振氢谱、碳谱和氟谱采用Bruker超导傅里叶数字化核磁共振仪(400 MHz, 德国)于室温下测定. 实验所需的无水无氧干燥溶剂大多经FLEANO溶剂纯化系统处理后得到, 实验所用其他试剂均为分析纯, 未经其他处理. 反应后处理均采用分析纯溶剂.

1.2 实验方法

(ⅰ) 化合物*E*-**1a**~**1q**的一般合成步骤. 在干燥的50 mL反应瓶中加入CuI(5 mol%), 然后抽空并用Ar回填(3次). 随后加入乙腈(10 mL)、五甲基二乙烯三胺(PMDETA, 7.5 mmol)、烯烃或杂芳烃(5 mmol)和溴二氟乙酸乙酯(7.5 mmol). 将反应物在油浴锅中搅拌12 h, 之后冷却至室温. 减压浓缩, 混合物经过硅胶柱层析纯化, 得到产物.

(ⅱ) 化合物*E*-**1r**~**1y**的一般合成步骤. 在氮气保护下, 将芳香丙烯醛(10 mmol)加入到干燥的50 mL反应瓶中, 然后用注射器加入2 mL二氯甲烷(DCM), 随后缓慢滴加二乙胺基三氟化硫(DAST, 20 mmol). 在40℃下搅拌混合物12 h后, 逐滴加入10 mL冷却水. 分离有机层, 并用DCM(2×20 mL)提取水层. 随后用H_2O(2×20 mL)洗涤合并的有机层, 并用无水Na_2SO_4干燥. 低温减压浓缩, 混合物经过硅胶柱层析分离得到产物.

(ⅲ) 反式二氟烯丙基化合物的一般合成步骤. 在干燥的反应管中依次加入乙酸乙酯(2.0 mL)、光催化剂2,4,5,6-四咔唑基-1,3-苯二腈(4CzIPN, 0.0032 g, 0.002 mmol)、反式烯丙基氟化物(0.20 mmol)、$NaHCO_3$(0.0017 g, 0.02 mmol), 将反应管置于30 W蓝色可见光照射下搅拌1 h. 反应结束后, 将反应液减压浓缩, 经柱层析分离得到顺式产物.

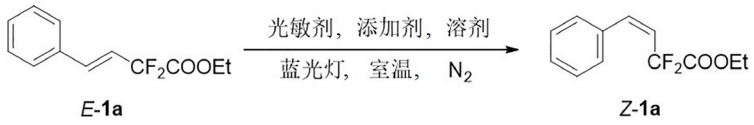
2 结果与讨论

2.1 反应条件的筛选及优化

以苯基烯丙基氟化物*E*-**1a**作为模板底物(三线态能量ET=53.5 kcal/mol), 探索了可见光促进的二氟烯丙基化合物异构化反应的最优反应条件(表1). 初步尝试的反应在以4CzIPN(ET=55.3 kcal/mol)为光催化剂, PhCOOK为碱, 四氢呋喃作为溶剂, 在30 W蓝色可见光照射下进行. 在该条件下, 能以68%的产率得到顺式二氟烯丙基化合物*Z*-**1a**(表1, 条目1). 控制实验表明, 无光照条件下, 没有反应发生(表1, 条目2). 当不添加光催化剂时, *Z*-**1a**的产率仅为10%(表1, 条目3). 不加入碱时, 反应的产率会有所下降(表1, 条目4). 根据相关报道, 碱的加入可以促进有机自由基中间体的产生[46,47], 因此我们对碱的类型进行了筛选. 当使用$NaHCO_3$作为添加剂时, *Z*-**1a**产率可以达到72%(表1, 条目5). 使用Et_3N、K_3PO_4、KOAc、NH_4HCO_3、PhCOONa作为碱时, 反应产率有所下降; 使用$KHCO_3$、NaOAc时, 反应产率有一定提升; 使用NaOH作为添加剂时, 没有获得目标产物(表1, 条目6~12). 其后, 我们对光催化剂的类型进行了考察. 根据三线态能量计算结果 当使用曙红 Y (Eosin Y, ET=69.3 kcal/mol)、三联吡啶氯化钌(Ru(bpy)$_3$Cl$_2$, ET=46.5 kcal/mol)、荧光素(fluorescein)作为光催化剂时, 反应没有发生, 使用(-)-核黄素、联苯甲酰(Benzil)、占吨酮(xanthone)作为光催化剂时, 仅能以低

表 1 反应条件研究[a)]

Table 1 Study of reaction conditions



E-**1a** *Z*-**1a**

条目	光催化剂	碱	溶剂	收率(%)[b)]
1	4CzIPN	PhCOOK	THF	68
2[c)]	4CzIPN	PhCOOK	THF	N.D.
3		PhCOOK	THF	10
4	4CzIPN		THF	55
5	4CzIPN	$NaHCO_3$	THF	72
6	4CzIPN	Et_3N	THF	50
7	4CzIPN	K_3PO_4	THF	25
8	4CzIPN	KOAc	THF	47
9	4CzIPN	NH_4HCO_3	THF	52
10	4CzIPN	PhCOONa	THF	63
11	4CzIPN	$KHCO_3$	THF	69
12	4CzIPN	NaOH	THF	N.D.
13	Eosin Y	$NaHCO_3$	THF	N.D.
14	$Ru(bpy)_3Cl_2$	$NaHCO_3$	THF	N.D.
15	荧光素	$NaHCO_3$	THF	N.D.
16	(-)-核黄素	$NaHCO_3$	THF	11
17	联苯甲酰	$NaHCO_3$	THF	24
18	占吨酮	$NaHCO_3$	THF	18
19	*fac*-Ir(ppy)$_3$	$NaHCO_3$	THF	70
20	4CzIPN	$NaHCO_3$	EtOAc	83
21	4CzIPN	$NaHCO_3$	MeCN	76
22	4CzIPN	$NaHCO_3$	1,4-二氧六环	76
23	4CzIPN	$NaHCO_3$	甲苯	78
24	4CzIPN	$NaHCO_3$	DMF	62
25	4CzIPN	$NaHCO_3$	MeOH	N.D.
26[d)]	4CzIPN	$NaHCO_3$	EtOAc	83
27[e)]	4CzIPN	$NaHCO_3$	EtOAc	82

a) 反应条件: *E*-**1a**(0.20 mmol)、光催化剂(0.004 mmol)、碱(0.40 mmol)和溶剂(2 mL), 在氮气保护的反应管中, 使用30 W 蓝色 LED灯室温照射. b) 使用胡椒环作为内标物通过粗产物的^{1}H NMR 测定产率. c) 避光. d) 0.02 mmol $NaHCO_3$. e) 0.002 mmol 4CzIPN. N.D. = 没有监测到

收率得到异构化产物(表1, 条目13~18). 这可能是因为这些光催化剂的三线态能量与芳基烯丙基氟化物的三线态能量相差较大, 不易发生能量转移导致[43]. 铱催化剂*fac*-Ir(ppy)$_3$与4CzIPN在当前反应中具有相同的催化活性(表1, 条目19). 随后, 我们考察了不同类型的溶剂对反应的影响. 将溶剂替换为EtOAc时, *Z*-**1a**产率可以达到83%(表1, 条目20). 使用MeCN、1,4-二氧六环、甲苯能使反应产率提升4%~6%. 将溶剂替换为DMF未能进一步提升反应收率, 而使用MeOH溶剂时, 反应没有发生(表1, 条目21~25). 最后, 对添加剂和光催化剂的用量进行了筛选. 当添加剂的用量减少到0.02 mmol时, 仍然可以以83%产率得到目标产物, 而催化剂的用量的减少会导致反应产率略微下降(表1, 条目26, 27).

2.2 反应适用性研究

在确定了最优的反应条件后, 我们对当前反应中

底物的适用性进行了考察. 首先考察了反式二氟烯丙基乙酸乙酯类化合物的适用性(图3). 当苯环上含有供电子取代基时, 随着供电子能力的增强, 顺式烯烃的产率随之下降. 取代基为甲基(*E*-**1b**)、叔丁基(*E*-**1c**)和甲氧基(*E*-**1d**)时, 分别能够得到70%、63%和65%的产率(*Z*-**1a**~**1d**). 含有氟、氯、溴的卤素取代基对反应的影响不大, 都能以高收率得到顺式二氟烯丙基目标产物(*Z*-**1e**~**1i**). 该反应能很好地适用于其他多种吸电子苯基底物, 包括氰基、硼酸基、硝基、酯基、苯基和三氟甲基(*Z*-**1j**~**1o**). 苄位含有取代基的底物在当前反应中也适用, 但反应产率有所降低(*Z*-**1p**). 使用含有杂环的顺式二氟烯烃底物, 当前反应能顺利进行并得到目标产物(*Z*-**1q**). 接着, 我们研究了反式二氟苯丙烯类化合物的适用性. 二氟苯丙烯及对甲基二氟苯丙烯、对甲氧基二氟苯丙烯都能以高收率转化为相应的顺式二氟苯丙烯(*Z*-**1r**~**1t**). 另外, 该类底物很少受到电子效应的影响, 多种含有吸电子取代基的底物都能顺利发生当前反应(*Z*-**1v**~**1y**). 值得一提的是, 该反应体系中没有副反应发生. 因此, 反应后剩余的原料*E*-**1**(反式二氟烯丙基化合物)可回收后再次通过该反应进行转化为*Z*-**1**(顺式二氟烯丙基化合物). 但是当使用乙基(*Z*)-2,2-二氟十二烷-3-烯酸丁酯未发生异构化反应, 提示当前反应体系并不适用于脂肪族的烯烃.

另外, 除反式二氟烯丙基化合物外, 当前光化学反应体系也能适用于反式苯乙烯类化合物的*E*→*Z*异构化(图4). 反式苯丙烯、反式肉桂醇、反式肉桂酸甲酯都发生了光催化异构化反应, 以良好的收率转化为相应的顺式产物, 提示当前反应体系具有广阔的适用范围.

2.3 反应应用研究

其后, 为了验证当前反应在制备大量制备*Z*-二氟烯丙基化合物中的实用性, 开展了克级反应(图5(a)). 当使用1.13 g *E*-**1a**作为底物时, 反应后能够分离得到0.88 g *Z*-**1a**, 分离产率为78%. 该实验说明当前反应适用于顺式二氟烯丙基化合物的大量制备. 我们还对顺式产物的衍生化进行了探究, 顺式产物*Z*-**1a**能在碱性条件下水解为相应的二氟烷基羧酸**3**, 也能被$NaBH_4$在室温下还原为二氟烷基醇**4**, 两类转化不仅收率高, 且

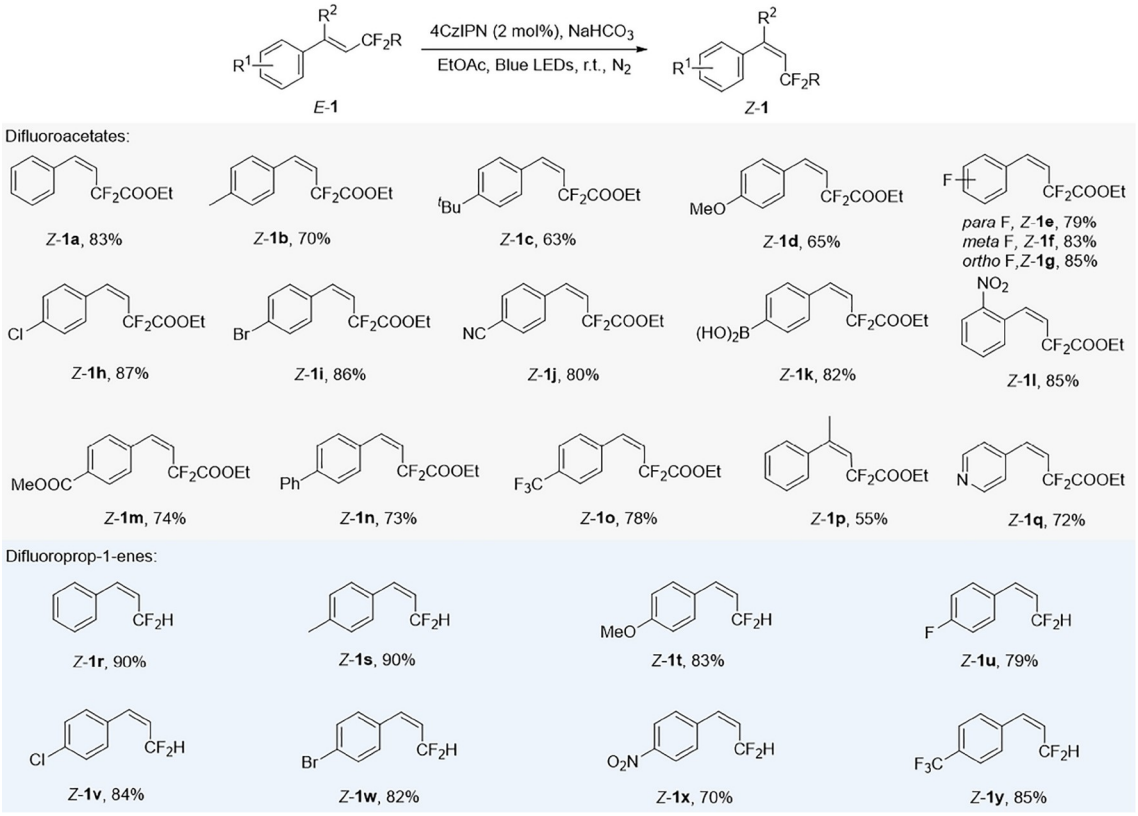


图 3 (网络版彩色)反式二氟烯丙基化合物适用性研究
Figure 3 (Color online) Substrate scope of trans allylic *gem*-difluorides

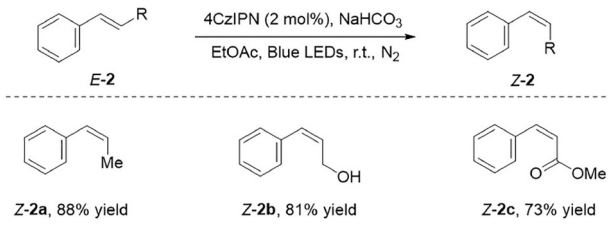


图 4 反式苯乙烯衍生物在反应体系中的适用性
Figure 4 Substrate scope of *trans*-styrenes

产物仍然保持为顺式构型(图5(b)), 为后续进一步转化为其他顺式二氟烯丙基衍生物提供了可能.

2.4 反应机理探究

为了解光催化异构化反应中*E*和*Z*构型之间的转化情况, 我们进行了动力学实验(图6). 在添加2 mol%光催化剂的标准条件下, 通过^{1}H NMR监测了反应物和异构化产物随时间变化的相对组成关系. 通过实验观察, 发现当前光化学反应进行很快, 在10 min就有67%转化为顺式二氟烯丙基产物*Z*-**1a**. 在40 min后不再进行异构化, 反应达到平衡状态. *E*和*Z*构型的二氟烯丙基的紫外吸收光谱显示, *E*-**1a**的最大吸收波长为259 nm, 与*Z*-

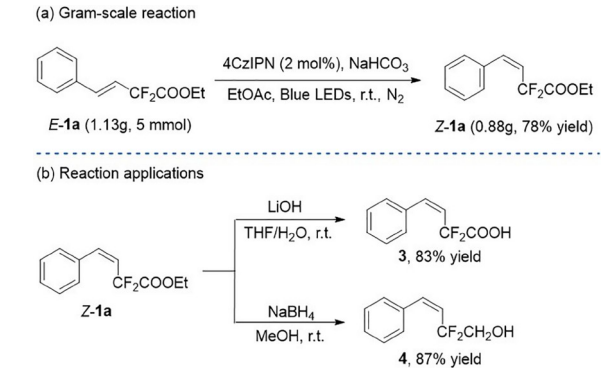


图 5 反应应用研究. (a) 克级反应; (b) 反应应用
Figure 5 Application of the reaction. (a) Gram-scale reaction; (b) reaction applications

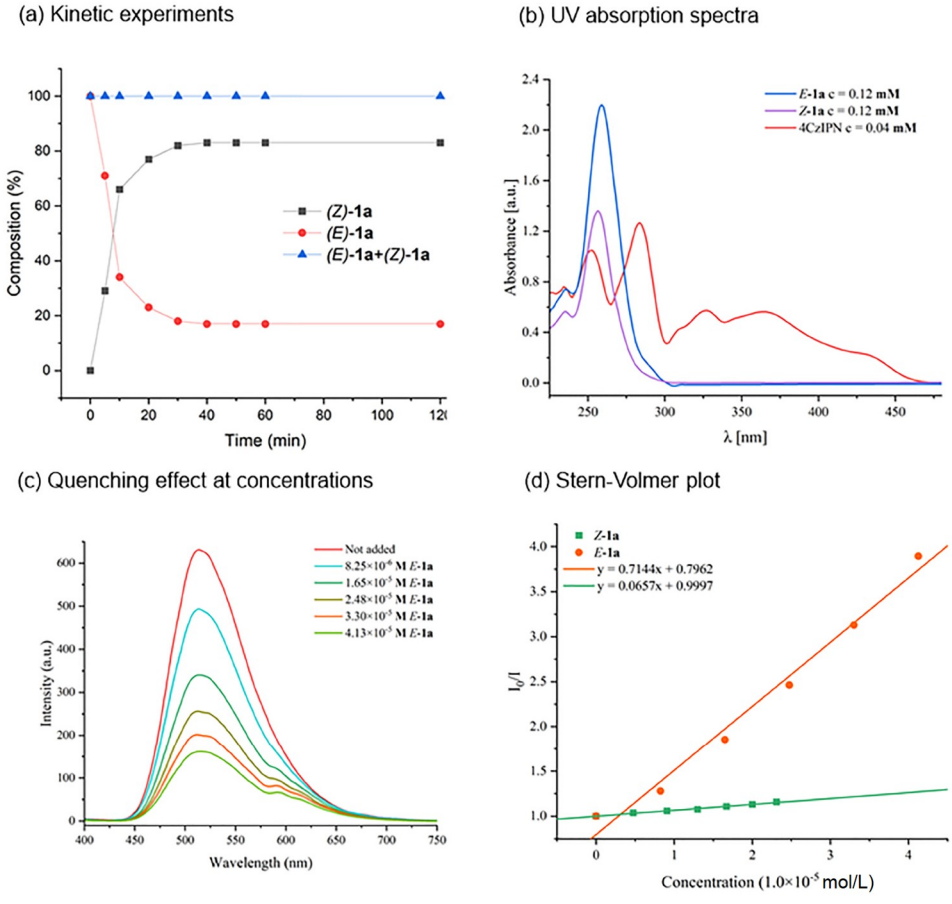


图 6 (网络版彩色)反应机理研究. (a) 动力学实验; (b) 紫外吸收光谱; (c) 浓度淬灭实验; (d) Stern-Volmer图
Figure 6 (Color online) Study of the reaction mechanism. (a) Kinetic experiments; (b) UV absorption spectra; (c) quenching effect at concentrations; (d) Stern-Volmer plot

1a的最大吸收波长(256 nm)接近, 但*E*-**1a**的吸收强度较*Z*-**1a**更强. 因二氟烯丙基化合物分子的能量与光催化剂激发态能量不匹配, 顺式二氟烯丙基化合物难以被光催化剂有效激发, 所以反应为正向进行, 产生动力学稳定的顺式二氟烯丙基化合物*Z*-**1a**. Stern-Volmer荧光淬灭实验显示, 不同浓度的反式二氟烯丙基产物*E*-**1a**对激发态光催化剂的淬灭效果随着*E*-**1a**浓度的变大而增大, 并且呈现出斜率为0.7144的良好线性关系.

通过上述实验及相关文献[34~41]报道, 我们提出了反应可能的机理(图7). 反应机理认为该反应是通过光激发下的光催化剂对反式二氟烯丙基化合物的能量转移完成. 首先, 光催化剂4CzIPN被光激发后, 从基态跃迁到激发态(PC*). *E*-**1a**经过TTET过程, 形成三线态的双自由基中间体*E*-**A**, 该中间体由于成键电子自旋方向相同具有不稳定的临界几何结构, 可以发生旋转得到中间体**A**, 其可经碳碳键自由旋转得到*Z*-**1a**或重新生成*E*-**1a**. 因三线态-三线态反应速率常数(k_{tt})较大[39], 由**A**得到*Z*-**1a**的反应具有显著优势, 从而得到顺式构型产物*Z*-**1a**.

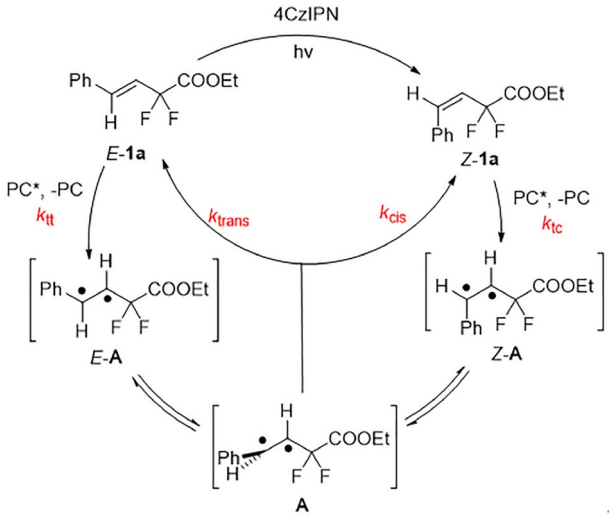


图 7 (网络版彩色)可能的反应机理

Figure 7 (Color online) Proposed reaction mechanism

3 结论

建立了以*E*-二氟烯丙基化合物选择性地得到了*Z*-二氟烯丙基化合物的方法. 该方法以4CzIPN为有机光催化剂催化, 适用于多种反式二氟烯丙基化合物和反式苯乙烯衍生物的***E*→*Z***异构化, 该方法反应体系简单、经济性好、反应条件温和并且能够实现该类化合物的大规模制备.

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Summary for “光促二氟烯丙基化合物的*E*→*Z*异构化反应”

Visible light promoted *E*→*Z* isomerization of difluoroallyl compounds

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Due to the unique properties of fluorine atoms, fluorinated organic compounds play significant roles in pharmaceuticals, pesticides, materials, fine chemicals, and other fields. About 25% of pharmaceuticals and 30% of pesticide molecules contain at least one fluorine atom. The fluorine atom has high electronegativity and a small atomic radius and is considered a bioisostere of the hydroxyl functional group in medicinal chemistry. Moreover, introducing fluorine atoms can significantly change lead compound’s solubility, hydrophobicity, metabolic stability, and bioavailability. Introducing a difluoroallyl group is essential for drug molecules, and the difluoroallyl compounds can be used as important intermediates in synthesizing other fluorinated compounds. Therefore, the synthesis method of difluoroallyl compounds has attracted extensive attention from the synthetic community. The radical coupling reaction of reactive olefins with halogenated difluoroalkanes was developed to synthesize difluoroallyl compounds. However, the current synthesis methods always afforded (*E*)-allyl difluoride as a main product.

The *cis* and *trans* olefins exhibit different physical and chemical properties and demonstrate different biological activities. Most of the synthesis methods of olefins mainly give the thermodynamic more stable trans olefins. Under heating conditions, *trans* olefins can be converted to *cis* olefins. In addition, *trans* and *cis* olefin mixtures are often challenging to be separated by column chromatography. Therefore, the highly selective synthesis of *cis* olefins is of great significance. Because the selective synthesis of thermodynamically unstable *cis* olefins is challenging, the conversion method from *trans* olefins to *cis* olefins has attracted much attention, which has a 100% atomic utilization rate and has been well developed in recent years. The transformation of geometric *cis*/*trans* isomerization of olefins is deeply embedded in organic photochemistry’s historical background and is currently experiencing renewed interest. However, the stereospecific *Z*/*E* isomerization of difluoroallyl compounds remains underdeveloped; thus, the selective *E*→*Z* photochemical isomerization for synthesizing (*Z*)-allyl difluoride exemplifies this growing trend.

During our study of the fluoroalkyl compound’s synthesis method, we disclosed the effective activation of (*E*)-difluoroallyl compounds with 4CzIPN as an organic photocatalyst under visible light irradiation and selectively obtained (*Z*)-difluoroallyl compounds. With the optimal reaction conditions in hand, we investigated the applicability of the substrates in the current reaction. By using aromatics that contain an electron-donor substituent, the yield of *cis* olefin decreases with the increase of electron-donating abilities of substituents. The substrates containing substituents such as fluorine, chlorine, and bromine had little effect on the reaction outcomes. The present reaction can be well applied to various substrates with other electron-withdrawing phenyl substrates. Substrates containing substituents at the benzyl position are also suitable for the current reaction, but the reaction yield is reduced. When a substrate containing a heterocycle is used, the current reaction can proceed smoothly, and the desired product can be obtained. It is worth noting that there are no side reactions in the reaction. Therefore, the remaining (*E*)-difluorallyl compounds can be recovered and converted into (*Z*)-difluorallyl compounds again through this reaction.

The developed photochemical reaction system can also suit the *E*→*Z* isomerization of *trans*-styrene compounds. *Trans*-phenylpropylene, *trans*-cinnamyl alcohol, and *trans*-cinnamate methyl ester all underwent present photocatalytic isomerization reactions, converted into corresponding *cis* products in good yields, demonstrating the broad application range of the current reaction. Also, the gram-scale reaction was carried out with a 78% yield, indicating that the current reaction is suitable for preparing (*Z*)-difluoroallyl compounds on a large scale. Further, the derivatization of *cis* products successfully gives the corresponding difluoroalkyl carboxylic acid and difluoroalkyl alcohol.

In conclusion, a visible light-promoted photocatalytic method was established to obtain (*Z*)-difluorallyl compounds from (*E*)-difluorallyl compounds selectively. 4CzIPN catalyzes this method as an organic photocatalyst suitable for the *E*→*Z* isomerization of various *trans*-difluoroallyl compounds and *trans*-styrene derivatives. This preparation method does not require a metal catalyst, is easy to operate, is mild and environmentally friendly, and could be used to prepare (*Z*)-difluoroallyl compounds on a large scale.

photocatalytic, isomerization, difluoroallyl, 4CzIPN

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