

申 报	系列：教师
	专业：化学
	职称：副教授

业绩成果材料

（申报人的业绩成果材料包括论文、科研项目、获奖以及其他成果等）

单 位（二级单位） 材料与能源学院

姓 名 杨波

材料核对人：

单位盖章：

核对时间：

华南农业大学制

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项目批准号	22001079
申请代码	B010703
归口管理部门	
依托单位代码	51064108A0498-0931



国家自然科学基金委员会 资助项目计划书

资助类别：青年科学基金项目

亚类说明：

附注说明：

项目名称：非活化三氟甲基取代芳烃的选择性C-F键切断/官能化反应

直接费用：24万元 执行年限：2021.01-2023.12

负责人：杨波

通讯地址：广东省广州市天河区五山路 381 号华南理工大学 15 号楼 141 室

邮政编码：510640 电 话：020-87111141

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依托单位：华南理工大学

联系人：伏琳 电 话：020-87112700

填表日期：2020年10月07日

国家自然科学基金委员会制



国家自然科学基金委员会资助项目计划书填报说明

- 一、项目负责人收到《关于国家自然科学基金资助项目批准及有关事项的通知》（简称《批准通知》）后，请认真阅读本填报说明，参照国家自然科学基金相关项目管理办法和《国家自然科学基金资助项目资金管理办法》（请查阅国家自然科学基金委员会官方网站首页“政策法规”栏目），按《批准通知》的要求认真填写和提交《国家自然科学基金委员会资助项目计划书》（简称《计划书》）。
- 二、填写《计划书》时要科学严谨、实事求是、表述清晰、准确。《计划书》经国家自然科学基金委员会相关项目管理部门审核批准后，将作为项目研究计划执行、检查和验收的依据。
- 三、《计划书》各部分填写要求如下：
 - （一）简表：由系统自动生成。
 - （二）摘要及关键词：各类获资助项目都应当填写中、英文摘要及关键词。
 - （三）项目组主要成员：计划书中列出姓名的项目组主要成员由系统自动生成，与申请书原成员保持一致，不可随意调整。如果批准通知中“项目评审意见及修改意见表”中“对研究方案的修改意见”栏目有调整项目组成员相关要求的，待项目开始执行后，按照项目成员变更程序另行办理。
 - （四）资金预算表：根据批准资助的直接费用，按照《国家自然科学基金项目预算表编制说明》填报资金预算表和预算说明书。国家重大科研仪器研制项目、重大项目还应按照预算评审后批复的直接费用各科目金额填报资金预算表、预算说明书及相应的预算明细表。国家杰出青年科学基金项目资助经费试行包干制管理，无需填报资金预算表和预算说明书。
 - （五）正文：
 1. 面上项目、青年科学基金项目、地区科学基金项目：如果《批准通知》中没有修改要求的，只需选择“研究内容和研究目标按照申请书执行”即可；如果《批准通知》中“项目评审意见及修改意见表”中“对研究方案的修改意见”栏目明确要求调整研究期限和研究内容等的，须选择“根据研究方案修改意见更改”并填报相关修改内容。
 2. 重点项目、重点国际（地区）合作研究项目、重大项目、国家重大科研仪器研制项目、原创探索计划项目：须选择“根据研究方案修改意见更改”，根据《批准通知》的要求填写研究（研制）内容，不得自行降低、更改研究目标（或仪器研制的技术性能与主要技术指标以及验收技术指标）或缩减研究（研制）内容。此外，还要突出以下几点：
 - （1）研究的难点和在实施过程中可能遇到的问题（或仪器研制风险），拟采用的研究（研制）方案和技术路线；
 - （2）项目主要参与者分工，合作研究单位（如有）之间的关系与分工，重大项目还需说明课题之间的关联；
 - （3）详细的年度研究（研制）计划。



3. 国家杰出青年科学基金、优秀青年科学基金和创新研究群体项目：须选择“根据研究方案修改意见更改”，按下列提纲撰写：
 - （1）研究方向；
 - （2）结合国内外研究现状，说明研究工作的学术思想和科学意义（限两个页面）；
 - （3）研究内容、研究方案及预期目标（限两个页面）；
 - （4）年度研究计划；
 - （5）研究队伍的组成情况。
4. 国家自然科学基金基础科学中心项目：须选择“根据研究方案修改意见更改”，应当根据评审委员会和现场考察专家组的意见和建议，进一步完善并细化研究计划，作为评估和验收的依据。按下列提纲撰写：
 - （1）五年拟开展的研究工作（包括主要研究方向、关键科学问题与研究内容）；
 - （2）研究方案（包括骨干成员之间的分工及合作方式、学科交叉融合研究计划等）；
 - （3）年度研究计划；
 - （4）五年预期目标和可能取得的重大突破等；
 - （5）研究队伍的组成情况。
5. 对于其他类型项目，参照面上项目的方式进行选择和填写。



简表

项目负责人信息	姓 名	杨波	性 别	男	出生年月	1990年02月	民 族	汉族
	学 位	博士			职称	博士后		
	是否在站博士后	是			电子邮件	sysuyb@163.com		
	电 话	020-87111141			个人网页			
	工 作 单 位	华南理工大学						
	所 在 院 系 所	化学与化工学院						
依托单位信息	名 称	华南理工大学					代码	51064108A0498
	联 系 人	伏琳			电子邮件	fulin@scut.edu.cn		
	电 话	020-87112700			网站地址	http://www.scut.edu.cn		
合作单位信息	单 位 名 称							
项目基本信息	项 目 名 称	非活化三氟甲基取代芳烃的选择性C-F键切断/官能化反应						
	资 助 类 别	青年科学基金项目				亚 类 说 明		
	附 注 说 明							
	申 请 代 码	B010703:光化学合成				B0107:绿色合成		
	基 地 类 别							
	执 行 年 限	2021.01-2023.12						
	直 接 费 用	24万元						



项目摘要

中文摘要:

含氟有机化合物因其特殊的物理生物化学性能在医药、农药和材料科学领域被广泛的应用, 构建有机氟化物成为科研工作者研究的热点。传统的含氟有机化合物主要是通过C-F键或者碳与含氟部分成键来构建。本项目利用三氟甲基芳香类化合物的缺电子特性, 通过单电子还原策略选择性实现C-F键的切断/官能化来构建 α, α -二氟苄基分子。本项目拟从以下几个方面开展工作: 1) 催化条件下光诱导的C-F键选择性切断/官能化反应研究; 2) 硅试剂辅助的光诱导的C-F键选择性切断官能化反应研究; 3) 反应机理研究。

本项目从绿色化学角度出发, 无需对底物进行预官能化, 具有很高的原子/步骤经济性, 为构建含氟有机化合物提供了新的策略。

Abstract:

Organofluorine compounds are an important class of molecules that are widely used in various fields, including the pharmaceutical sciences, agrochemistry, and materials science due to their unique physicochemical and biological properties. Traditionally, organofluorine compounds are prepared through construction of carbon-fluorine (or moieties including fluorine atoms) bond. This project is intended to realize the construction of difluorobenzyl arrays through selective carbon-fluorine bond cleavage of trifluoromethylaromatic motifs via single electron transfer (SET) based on the poor electron density. The project is consisted of the following three aspects: 1) Visible-light promoted selective carbon-fluorine bond cleavage/functionalizations of trifluoromethylaromatic motifs via a catalytic way; 2) Silicon-based reagent promoted selective carbon-fluorine bond cleavage/functionalizations of trifluoromethylaromatic motifs via exciplex; 3) Mechanistic studies.

The project will provide a novel strategy to construct difluorobenzyl compounds without pre-functionalizations, which is in consistent with the concept of green chemistry.

关键词(用分号分开): 有机光化学; 自由基反应; 选择性切断; 官能化; 二氟甲基芳烃

Keywords(用分号分开): organic photochemistry; radical reaction; selective cleavage; functionalization; difluorobenzyl derivatives



项目组主要成员

编号	姓名	出生年月	性别	职称	学位	单位名称	电话	证件号码	项目分工	每年工 作时间 (月)	
1	杨波	1990.02	男	博士后	博士	华南理工大学	020-87111141	34032219900216 2438	项目负责人	10	
总人数			高级		中级		初级		博士后	博士生	硕士生



国家自然科学基金项目直接费用预算表（定额补助）

项目批准号：22001079

项目负责人：杨波

金额单位：万元

序号	科目名称	金额
1	项目直接费用合计	24.0000
2	1、设备费	2.0000
3	(1)设备购置费	2.00
4	(2)设备试制费	0.00
5	(3)设备升级改造与租赁费	0.00
6	2、材料费	7.20
7	3、测试化验加工费	6.30
8	4、燃料动力费	1.50
9	5、差旅/会议/国际合作与交流费	1.50
10	6、出版/文献/信息传播/知识产权事务费	1.00
11	7、劳务费	3.60
12	8、专家咨询费	0.00
13	9、其他支出	0.90



预算说明书（定额补助）

（请按照《国家自然科学基金项目预算表编制说明》等的有关要求，对各项支出的主要用途和测算理由，以及合作研究外援资金、单价 ≥ 10 万元的设备费等内容进行必要说明。）

项目申请直接经费24万元：

1. 设备费2万元：用于购买实验室易耗小型仪器，如旋蒸，真空泵，低温浴，搅拌器等，以及实验室仪器的常规维修费用。
2. 材料费7.2万元：用于购买项目所需贵金属催化剂，化学药品，有机溶剂和气体等，种类多，用量大，费用高。
3. 测试化验加工费6.3万元：用于分析测试收费，包括核磁氢谱（至少1000个/年），碳谱（至少200个/年），高分辨质谱（至少100个/年），单晶衍射（3-5个/年），以及元素分析、红外等表征，种类多，用量大，费用高。
4. 燃料动力费1.5万元：大型仪器设备、专用科学装置等运行的水、电、气、燃料消耗费用等。
5. 差旅/会议/国际合作与交流费1.5万元：用于参加国内外学术会议，学术交流费用，包括车费，机票，住宿，注册费等，国内预算约4000元/人次，共计4人次，总计1.5万元。
6. 出版/文献/信息传播/知识产权事务费1万元：用于专利申请费，论文编辑、版面费等。
7. 劳务费3.6万：用于参加项目研究生的部分科研补助。
3名硕士生： $(400\text{元/人月} \times 10\text{月/年} \times 3\text{年}) \times 3 = 3.6$ 万元
9. 其他支出0.9万元：打印资料所需的耗材费等其他科研支出。



报告正文

研究内容和研究目标按照申请书执行。

国家自然科学基金资助项目签批审核表

<p>我接受国家自然科学基金的资助，将按照申请书、项目批准意见和计划书负责实施本项目（批准号：22001079），严格遵守国家自然科学基金委员会关于资助项目管理、项目资金管理等各项规定，切实保证研究工作时间，认真开展研究工作，按时报送有关材料，及时报告重大情况变动，对资助项目发表的论著和取得的研究成果按规定进行标注。</p> <p>项目负责人（签章）：杨波 2020年10月21日</p>	<p>依托单位科研管理部门：</p> <p>负责人（签章）： 年 月 日</p>														
	<p>依托单位财务管理部门：</p> <p>负责人（签章）： 2020年10月23日</p>														
<p>我单位同意承担上述国家自然科学基金项目，将保证项目负责人及其研究队伍的稳定和研究项目实施所需的条件，严格遵守国家自然科学基金委员会有关资助项目管理、项目资金管理等各项规定，并督促实施。</p> <p>依托单位（公章） 2020年10月23日</p>															
本栏目由基金委填写	<p>科学处审查意见：</p> <p>同意按计划执行</p> <p>建议年度拨款计划（本栏目为自动生成，单位：万元）：</p> <table border="1" data-bbox="215 1164 1037 1288"> <thead> <tr> <th>年度</th> <th>总额</th> <th>第一年</th> <th>第二年</th> <th>第三年</th> <th>第四年</th> <th>第五年</th> </tr> </thead> <tbody> <tr> <td>金额</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>负责人（签章）： 2020年11月30日</p>	年度	总额	第一年	第二年	第三年	第四年	第五年	金额						
	年度	总额	第一年	第二年	第三年	第四年	第五年								
金额															
<p>科学部审查意见：</p> <p>同意科学处意见</p> <p>负责人（签章）： 年 月 日</p>															
本栏目主要用于重大项目等	<p>相关局室审核意见：</p> <p>负责人（签章）： 年 月 日</p>														
	<p>委领导审批意见：</p> <p>委领导（签章）： 年 月 日</p>														

国家自然科学基金资助项目签批审核表

<p>我接受国家自然科学基金的资助，将按照申请书、项目批准意见和计划书负责实施本项目（批准号：22001079），严格遵守国家自然科学基金委员会关于资助项目管理、项目资金管理等各项规定，切实保证研究工作时间，认真开展研究工作，按时报送有关材料，及时报告重大情况变动，对资助项目发表的论著和取得的研究成果按规定进行标注。</p> <p>项目负责人（签章）：杨波 2020年10月21日</p>	<p>依托单位科研管理部门：</p> <p>负责人（签章）： 年 月 日</p>														
	<p>依托单位财务管理部门：</p> <p>负责人（签章）： 2020年10月23日</p>														
<p>我单位同意承担上述国家自然科学基金项目，将保证项目负责人及其研究队伍的稳定和研究项目实施所需的条件，严格遵守国家自然科学基金委员会有关资助项目管理、项目资金管理等各项规定，并督促实施。</p> <p>依托单位（公章） 2020年10月23日</p>															
本栏目由基金委填写	<p>科学处审查意见：</p> <p>同意按计划执行</p> <p>建议年度拨款计划（本栏目为自动生成，单位：万元）：</p> <table border="1"> <thead> <tr> <th>年度</th> <th>总额</th> <th>第一年</th> <th>第二年</th> <th>第三年</th> <th>第四年</th> <th>第五年</th> </tr> </thead> <tbody> <tr> <td>金额</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table> <p>负责人（签章）： 2020年11月30日</p>	年度	总额	第一年	第二年	第三年	第四年	第五年	金额						
年度	总额	第一年	第二年	第三年	第四年	第五年									
金额															
<p>科学部审查意见：</p> <p>同意科学处意见</p> <p>负责人（签章）： 年 月 日</p>															
本栏目主要用于重大项目等	<p>相关局室审核意见：</p> <p>负责人（签章）： 年 月 日</p>														
	<p>委领导审批意见：</p> <p>委领导（签章）： 年 月 日</p>														



资助证书

华南理工大学 杨波 (全国博管会编号:229423) 获得中国博士后科学基金
第68批面上资助二等。资助编号: 2020M682694。

特颁此证。

The certificate certifies its holder is awarded the fellowship of China Postdoctoral
Science Foundation .



中国博士后科学基金会
2020 年 11 月 03 日

受理编号：SL2024A04J00151

广州市科技计划项目 申报书

项目名称：	活性氢自由基的可控生成及其在合成上的应用
申报单位：	华南农业大学
项目负责人：	杨波
计划类别：	基础研究计划
专题名称：	2025年度基础与应用基础研究专题
支持方向：	青年博士“启航”项目
组织单位：	华南农业大学
起止时间：	2025-01-01 至 2026-12-31
主管处室：	引进智力管理处（科技人才处）

广州市科学技术局制

二〇二四年

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一、基本信息

项目 基本 信息	项目名称	活性氢自由基的可控生成及其在合成上的应用		
	学科领域1	化学综合处-有机化学-有机合成-有机合成反应		
	学科领域2	化学综合处-有机化学-绿色有机化学-无		
	指南发布日	2024年4月15日		
	申请市级财政 金额	5万元	研究期限	2025年1月1日- 2026年12月31日
项目 摘要	氢自由基寿命短、活性高，缺乏可控的产生方法，导致鲜有基于氢自由基策略发展合成化学的报道。本项目旨在利用芳构化驱动策略实现氢自由基的可控产生并开展其在合成上的应用研究。本项目拟从以下两个方面开展工作：1) 芳构化驱动产生氢自由基及其诱导的官能化反应；2) 反应机理研究。本项目在设计理念上系统提出基于芳构化驱动产生氢自由基的策略，并基于其发展新的碳自由基生成途径，为碳自由基的高效官能化提供了新的思路。			

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	联系人	姓名	倪慧群	
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	开户银行	广东广州工行五山支行		
	开户户名	华南农业大学		
银行账号	3602002609000310520			

三、项目负责人信息

姓名	杨波	证件类型	身份证
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学位	博士	学位授予国家 (或地区)	中国
职务	教师	职称	无
所学专业	化学	手机号码	18818914392
办公电话	020-85280319	电子邮箱	boyang@scau.edu.cn

四、项目经费信息

本项目总投入：¥（5）万元，其中，市财政科技经费：¥（5）万元，自筹经费：¥（0）万元。

1. 经费下达计划			
资金来源	小计	市财政科技经费	自筹经费
2025	5	5	0
总计	5	5	0

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申请人:	杨波
承担申报单位:	华南农业大学
项目名称:	活性氢自由基的可控生成及其在合成上的应用
专题方向:	2025年度基础与应用基础研究专题-青年博士“启航”项目
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日期：2024年05月06日

审核通过

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承担单位：华南农业大学

日期：2024年05月06日

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承担单位意见：

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日期：2024年05月24日

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日期：2024年07月11日

审核通过

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序号	论文名称	发表刊物及发表的年月卷期/页码等	作者排名	论文等级	作者工作单位	收录情况	影响因子	中科院大类分区
1	Diverse synthesis of C2-linked functionalized molecules via molecular glue strategy with acetylene	NATURE COMMUNICATIONS 出版年: 2022 出版日期: APR 6 卷期: 13 1 页码: - 文献号: 1858 文献类型: Article	第一作者	T2 类	华南理工大学 化学与化工学院	SCI	IF2-year=16.6 IF5-year=17.0 (2022)	综合性期刊 1 区 Top 期刊: 是 (2022)
2	Hydrogen radical-shuttle (HRS)-enabled photoredox synthesis of indanones via decarboxylative annulation	NATURE COMMUNICATIONS 出版年: 2021 出版日期: SEP 6 卷期: 12 1 页码: - 文献号: 5257 文献类型: Article	第一作者	T2 类	华南理工大学 化学与化工学院	SCI	IF2-year=17.694 IF5-year=17.764 (2021)	综合性期刊 1 区 Top 期刊: 是 (2021)
3	Direct synthesis of dialkyl ketones from deoxygenative cross-coupling of carboxylic acids and alcohols	CHEMICAL SCIENCE 出版年: 2024 出版日期: NOV 13 卷期: 15 44 页码: 18405-18410 文献类型: Article	第一作者	T2 类	华南农业大学 材料与能源学院	SCI	IF2-year=7.4 IF5-year=7.8 (2024)	化学 1 区 Top 期刊: 是 (2025)



4	Bifunctional two-carbon reagent made from acetylene via 1,2-difunctionalization and its applications	SCIENCE CHINA-CHEMISTRY 出版年: 2024 出版日期: MAR 卷期: 67 3 页码: 936-944 文献类型: Article	第一作者	T2 类	华南理工大学 化学与化工学院	SCI	IF2-year=9.7 IF5-year=8.4 (2024)	化学 1 区 Top 期刊: 是 (2025)
5	Visible Light-Promoted Three-Component Carboazidation of Unactivated Alkenes with TMSN ₃ and Acrylonitrile	CHINESE JOURNAL OF CHEMISTRY 出版年: 2018 出版日期: NOV 卷期: 36 11 页码: 1017-1023 文献类型: Article	第一作者	B 类	浙江大学化学系	SCI	IF2-year=2.376 IF5-year=1.679 (2018)	化学 4 区 Top 期刊: 否 (2018)

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OPEN

Diverse synthesis of C2-linked functionalized molecules via molecular glue strategy with acetylene

Bo Yang ¹, Shaodong Lu², Yongdong Wang ² & Shifa Zhu ¹✉

As the simplest alkyne and an abundant chemical feedstock, acetylene is an ideal two-carbon building block. However, in contrast to substituted alkynes, catalytic methods to incorporate acetylene into fine chemicals are quite limited. Herein, we developed a photoredox-catalyzed synthetic protocol for diverse C2-linked molecules via a molecular glue strategy using gaseous acetylene under mild conditions. Initiated by addition of an acyl radical to acetylene, two cascade transformations follow. One involves a double addition for the formation of 1,4-diketones and the other where the intermediate vinyl ketone is intercepted by a radical formed from a heterocycle. In addition to making two new C-C bonds, two C-H bonds are also created in two mechanistically distinct ways: one via a C-H abstraction and the other via protonation. This system offers a reliable and safe way to incorporate gaseous acetylene into fine chemicals and expands the utility of acetylene in organic synthesis.

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As the simplest alkyne, acetylene has traditionally been viewed more as a fuel than as an economical chemical feedstock, though it is widely used in chemical industry, with an estimated annual global production of over one million tons¹. The high-volume industrial use of acetylene includes the production of vinyl-containing monomers, such as vinyl amine, vinyl chloride, acrylic acid and its derivatives, used for polymeric materials, in other chemical commodities and as feedstocks^{2–4}. The spatial orthogonality of the two independent π -systems in alkynes can be used for the discovery, design and control of the new cascade transformations⁵. However, in contrast to other substituted alkynes, a very limited number of catalytic protocols directly incorporate acetylene into fine chemicals. This is probably due to the greater inherent strength of the π -bonds⁵, higher activation energies for reactions⁵ and, especially, apprehensions about handling an explosive⁶ and flammable gaseous reagent. In fact, reactions exploiting acetylene at atmospheric pressure (1 atm) are uncommon^{1–4,7–14}. Moreover, the instability of its possible intermediates, the terminal vinyl radical^{15,16} and, especially, the cation¹⁷ has traditionally restricted its conversion. Circumvention of these obstacles would undoubtedly boost the use of acetylene as a reagent in modern organic synthesis involving complex small molecules. Currently, the catalytic transformations of acetylene into fine chemicals are mainly focused on simple mono-functionalizations, such as vinylation^{2,3,7–10,13,14,18,19}, the Sonogashira coupling reaction^{20,21}, and cyclization^{2,22}. In addition, construction of other molecules with different levels of molecular complexity^{11,12,21–23} is of interest (Fig. 1a). To effectively introduce acetylene in synthesis, competing reactions, such as the generation of more reactive substituted alkynes or alkenes from acetylene, need to be avoided. Despite elegant synthetic developments, effective catalytic strategies to incorporate acetylene gas into fine chemicals remain scarce.

A variety of structurally complex and biologically active molecules or their precursors can be regarded as two components linked with a saturated two-carbon unit^{24–26} (Fig. 1b). Ideally, it would be desirable to bridge two or more simple molecules simply through their exposure to a C2-synthon in the presence of a catalyst. This would provide an efficient platform to quickly construct the target molecules and offer molecular diversity via the molecular glue strategy²⁷. As the simplest and abundant unsaturated two-carbon molecular building units, ethylene^{12,28,29} and acetylene^{2,3,7–12,18–23} have been employed as C2 building blocks for the formation of fine chemicals. In fact, due to the presence of two addressable π -systems, acetylene can be used as a carbon glue³⁰, a type of molecular glue, that connects molecules through sequential transformations of the two π -bonds, which mutually complements the ethylene transformation field^{12,28,29,31,32} (Fig. 1c). Given 1,4-diketones have great importance as versatile intermediates for the synthesis of some bioactive molecules³³, natural products and related compounds^{34,35}, along with the ubiquity of bioactive molecules containing a carbonyl group linked to a heterocycle moiety²⁶ by a $\text{CH}_2\text{-CH}_2$ bridge, developing a general methodology to quickly access these compounds via a molecular glue strategy from readily available molecules and abundant feedstock would be highly desirable, especially in drug discovery chemistry³⁶.

Photocatalysis has recently emerged as a powerful platform for the direct functionalization and activation of organic compounds via open-shell pathways under mild conditions^{37–42}. As one of the most widely exploited transformations within the realm of open-shell chemistry, the direct addition of carbon radicals to carbon-carbon π -bonds has been broadly leveraged to effect carbon-carbon bond formation with alkenes^{43,44}. Encouraged by these developments, we wondered if it is feasible to utilize the highly reactive terminal vinyl radical, generated through the acyl radical addition to acetylene, to accomplish the C-H abstraction

from suitable hydrogen donors, followed by a Giese radical addition^{45–49}, resulting in the formation of 1,4-diketones or connecting the carbonyl group to heterocycles via a two-carbon unit (Fig. 1d). However, the direct addition of most common radicals to unactivated alkynes, especially acetylene, to obtain the terminal vinyl radical, is a really big challenge due to (i) the diminished rate of C-C bond formation owing to increased activation barriers^{15,50,51} and (ii) the in situ generation of high-energy vinyl radical intermediates that are highly unstable, have a short lifetime, and readily participate in various undesirable open-shell pathways. To the best of our knowledge, direct addition to acetylene producing a terminal vinyl radical followed by functionalization is rarely reported⁵². In addition, the various radicals formed can react with the acetylene or the newly formed alkene generating undesired products. Importantly, how to selectively generate the desired product is also a big problem. Using the polarity matching effect, a subtle yet important element in radical addition process⁵³, the generated product may be controlled by varying the electronic properties of the hydrogen donors. In addition, side reactions may be limited by quenching the radical intermediate formed by the C-H abstraction from the hydrogen donor.

In this work, we developed a photoredox-catalyzed synthetic protocol for diverse C2-linked molecules via a molecular glue strategy that employed gaseous acetylene under mild conditions (Fig. 1e). Formally, aryl ketones were linked to aryl ketones, or linked with heterocycles by $\text{CH}_2\text{-CH}_2$ bridges, resulting in the formation of two C-C bonds and two C-H bonds. Mechanistic experiments demonstrate that the two C-H bonds are created in two mechanistically distinct ways, one via a C-H abstraction and the other via protonation.

Results and discussion

Reaction development. To start our investigation, the synthetic method for 1,4-diketones was explored with the commercially available α -oxocarboxylic acid **1a** as the model substrate, acetylene gas as the C2-linker reagent, K_2HPO_4 as the base, H_2O as the hydrogen source and $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{dtbpy})\text{PF}_6$ as the visible-light photocatalyst at room temperature under the irradiation of blue LEDs. From a mechanistic perspective, the highly reactive vinyl radical should abstract a hydrogen atom from a solvent $\text{Csp}^3\text{-H}$ bond because of the $\text{Csp}^2\text{-H}$'s higher bond dissociation energy (BDE)^{54,55}. To our delight, the reaction in a solution of DCM/ H_2O (v/v) (3/2) afforded the desired 1,4-diketone **2a** in 10% yield (Table 1, entry 1). Examination of a range of photocatalysts revealed that $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$ was superior with respect to reaction efficiency, yielding **2a** in 16% yield (entries 2–4). Various solvents, such as acetone, *N,N*-dimethylformamide, acetonitrile, and tetrahydrofuran, were used instead of dichloromethane (entries 5–8) and the results indicated dichloromethane was more suitable for this transformation. The concentration of **1a** and the amount of water may affect the reaction efficiency. When **1a** was decreased to 0.05 M, 38% isolated yield of **2a** was obtained (H_2O (5 equiv.), 24 h) (entry 9). Prolonging the reaction time (36 h) did not improve the yield of **2a** (entry 10). Further reducing **1a** to 0.025 M improved the yield to 51% (entry 11). A slight decrease in the yield was observed when the concentration was further reduced (entry 12). Using other inorganic bases did not positively affect the reaction efficiency (entries 13–15). Gratifyingly, the yield of **2a** could be greatly improved to 79% by increasing H_2O (20 equiv.) (entry 16). Further increasing the amount of water decreased the yield (entry 17), which means the amount of water has an important effect on the yield.

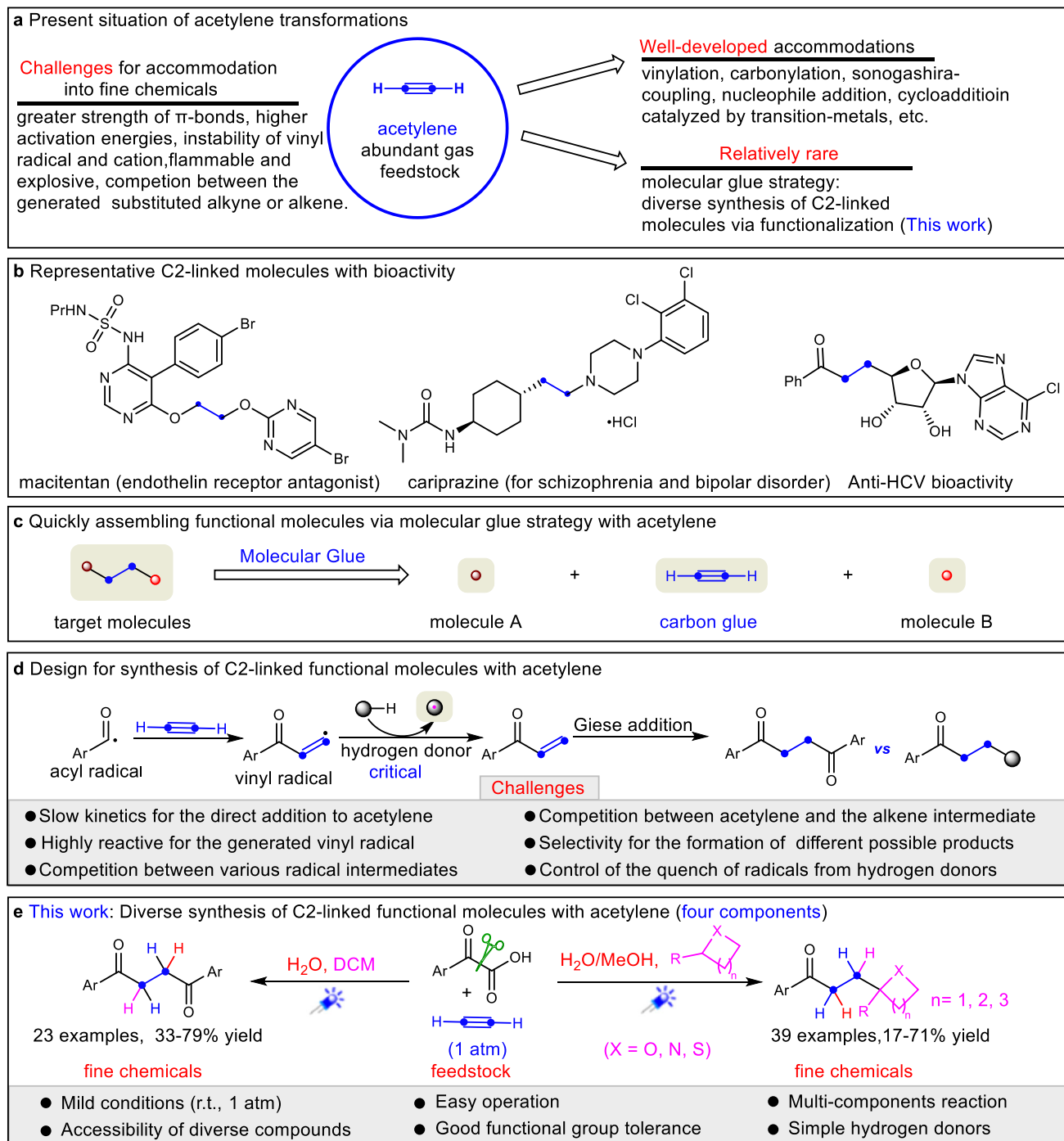


Fig. 1 Synthesis of C2-linked molecules with acetylene via molecular glue strategy. **a** Present situation of acetylene transformations. **b** Representative C2-linked molecules with bioactivity. **c** Quickly assembling functional molecules via a molecular glue strategy with acetylene. **d** Design for synthesis of C2-linked molecules with acetylene. **e** Diverse synthesis of C2-linked molecules with acetylene. DCM, Dichloromethane.

Reaction scope investigation. With the optimal reaction conditions in hand (Table 1, entry 16), we next investigated the scope of a variety of α -oxocarboxylic acids summarized in Fig. 2. The *o*-, *m*- and *p*-methyl groups on phenyl α -oxocarboxylic acids were tolerated (**2b-d**). A number of phenyl α -oxocarboxylic acids bearing electron-donating groups, including not only 1°-alkyl groups but also more hindered 2°- and 3°-alkyl groups, were converted into the corresponding 1,4-diketones in good yields (**2e-l**). The 3,5-dimethyl substituted substrates was transformed into the desired compound in 68% yield (**2m**). Halogenated phenyl substrates were incorporated into the corresponding

compounds with slightly lower yields (43-66%) (**2n-q**). The phenyl α -oxocarboxylic acid bearing a strong electron-withdrawing group underwent smoothly to afford **2r** in 50% yield. Notably, 2-(2,3-dihydro-1*H*-inden-5-yl)-2-oxoacetic acid **1s** and 2-oxo-2-(5,6,7,8-tetrahydronaphthalen-2-yl) acetic acid **1t** provided the corresponding **2s** and **2t** in moderate yields. Importantly, the methoxy-substituted long chain substrate **1u** was also suitable for this transformation giving **2u** in moderate yield. Moreover, the 2-adamantanol-derived α -oxocarboxylic acid **1v** and L-menthol-derived α -oxocarboxylic acid **1w** reacted smoothly under the standard conditions to furnish the

Table 1 Optimization of the Reaction Conditions.

Entry	PC	Base	Solvent	Yield (%) ^a
1	Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆	K ₂ HPO ₄	DCM/H ₂ O (3/2) (0.1 M)	10%
2	4CzIPN	K ₂ HPO ₄	DCM/H ₂ O (3/2) (0.1 M)	0
3	Eosin Y	K ₂ HPO ₄	DCM/H ₂ O (3/2) (0.1 M)	0
4	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DCM/H ₂ O (3/2) (0.1 M)	16
5	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	Acetone/H ₂ O (3/2) (0.1 M)	0
6	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DMF/H ₂ O (3/2) (0.1 M)	0
7	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	MeCN/H ₂ O (3/2) (0.1 M)	<10
8	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	THF/H ₂ O (3/2) (0.1 M)	<5
9 ^b	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DCM (0.05 M)	38
10 ^c	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DCM (0.05 M)	34
11 ^b	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DCM (0.025 M)	51
12 ^b	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DCM (0.017 M)	44
13 ^b	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ CO ₃	DCM (0.025 M)	26
14 ^b	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	KF	DCM (0.025 M)	49
15 ^b	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₃ PO ₄	DCM (0.025 M)	19
16 ^d	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DCM (0.025 M)	79
17 ^e	Ir[dF(CF ₃)ppy] ₂ (phen)PF ₆	K ₂ HPO ₄	DCM (0.025 M)	49

Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆

Ir[dF(CF₃)ppy]₂(phen)PF₆

R = carbazolyl
4CzIPN

Eosin Y

^a1a (0.3 mmol). Yields of 2a were determined by ¹H NMR with mesitylene as an internal standard. ^bH₂O (5 equiv.), 24 h, isolated yield. ^cH₂O (5 equiv.), 36 h, isolated yield. ^dH₂O (20 equiv.), 24 h, isolated yield. ^eH₂O (40 equiv.), 24 h, isolated yield. dF(CF₃)ppy, 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl; phen, o-Phenanthroline; DCM, Dichloromethane; equiv., equivalent; PC, photocatalyst.

corresponding desired compounds **2v** and **2w** in moderate yields. These results show a great potential for the structural modification of an array of complex biological molecules in medicinal chemistry. Notably, various experiments with substrates containing redox non-innocent substituents, such as amino-, phenolic hydroxyl-, vinyl-, alkynyl- and hydroxyl-substituted, were also performed under the standard conditions. Unfortunately, these functional groups were not compatible with our system.

Considering these results, we turned our attention to test other hydrogen donors, specifically nucleophilic hydrogen donors. These donors would generate radical intermediates from C-H abstractions by the highly reactive vinyl radicals. The resulting C-H abstracted radical intermediate reacted well with the electron-deficient alkenes^{44–48} to furnish the desired compounds containing the carbonyl group and nucleophilic component linked via a CH₂-CH₂ bridge. In 2016, Knowles⁵⁶ reported an elegant intermolecular C-H functionalization to construct similar molecules in moderate yields using stoichiometric *N*-ethyl-4-methoxybenzamide as the abstractor. This abstractor has the potential to serve as a structurally modular catalyst for radical C-H functionalization. Though powerful, the preparation of the vinyl ketone and additional reagents to activate the substrate were required for the reported method. If the vinyl radical generated in our system could be used as the abstractor, it would be highly desirable. Due to the prevalence of furan-containing compounds^{57,58}, THF was subsequently explored as a hydrogen

donor and furan source, as well as the solvent. In fact, 13% yield of the tetrahydrofuran linked compound was isolated during the optimization (Table 1, entry 8). A considerable increase in yield was obtained with a slight variation of the reaction conditions (Fig. 3). With respect to the 2-aryl-2-oxocarboxylic acid partner, we observed moderate to good yields of the desired products, which represent an important skeleton in a variety of bioactive molecules¹¹. 2-Oxo-2-phenyl-acetic acids bearing both electron-donating and electron-withdrawing substituents on the phenyl ring are suitable substrates (**3a–3ab**). Relatively lower yields were observed when an electron-withdrawing group was attached to the phenyl ring (**3r–u**), which could be ascribed to the reduced reductive quenching ability toward the photoexcited photocatalyst. Notably, 2-aryl-2-oxocarboxylic acids with synthetic handles, such as halides, were readily incorporated into the products (**3t–u**), which highlights the potential for the incorporation of these scaffolds into more complex targets. Evaluation of substrates containing reactive groups, such as the chemically and biologically abundant amide and ester, provided the corresponding products in moderate yield (**3x–3z**). The starting material, bearing an easily-oxidized thioether, is also tolerated in this system, furnishing the desired product **3aa** in moderate yield. In addition, 2-naphthyl- and 1-fluorene-substituted glyoxylic acids are both suitable substrates, albeit in slightly lower yield (**3ac–3ad**). The reactive benzylic C-H bonds in the starting material, or in the corresponding product **3ad**, remain intact under the reaction

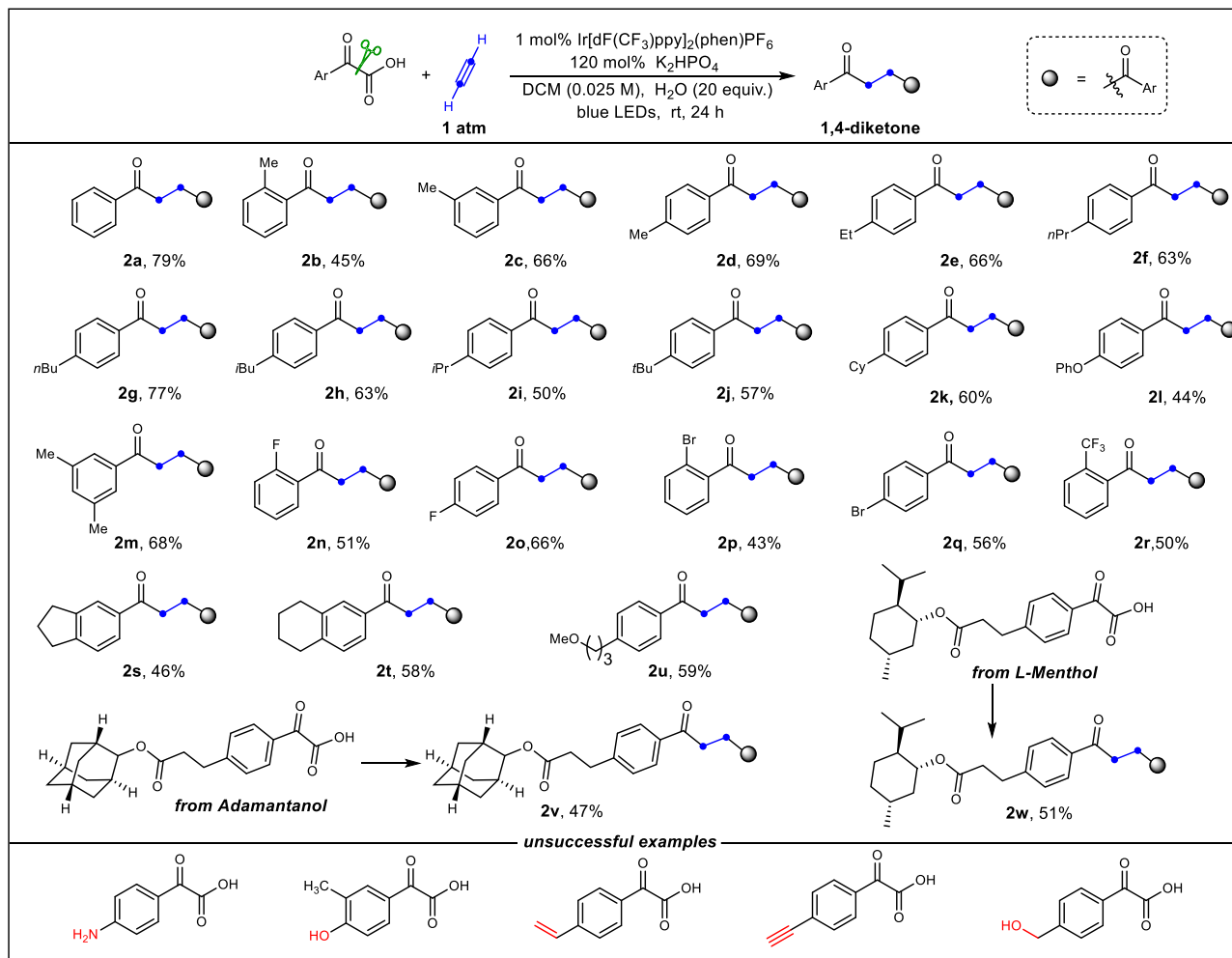


Fig. 2 Substrate scope for 1,4-diketones synthesis. Standard conditions: α -Oxocarboxylic Acid (0.3 mmol), Ir[dF(CF₃)ppy]₂(Phen)PF₆ (0.01 equiv.), H₂O (20 equiv.) in a solution of DCM (0.025 M) under the irradiation of blue LEDs under acetylene gas for 24 h at room temperature. Isolated yield of products. dF(CF₃)ppy, 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl; phen, o-Phenanthroline; DCM, Dichloromethane; equiv., equivalent.

conditions. The simple benzoylformic acid was transformed to the corresponding product **3ae** in 69% yield. Moreover, the menthol-derived α -oxocarboxylic acid and 2-adamantanol-derived α -oxocarboxylic acid reacted smoothly under the standard conditions to furnish the desired compounds **3af** and **3ag** in moderate yield. These results show the potential for the structural modification of an array of bioactive molecules.

Considering the experimental results above and the requirements for construction of other heterocycle-containing compounds as well as the extension of this approach, some hydrocarbons, especially, heterocycles instead of tetrahydrofuran were subsequently tested (Fig. 4). It was found that this strategy could also be adapted for use with other five-membered heterocycle-based hydrogen donors (Fig. 4a). When substituted tetrahydrofuran was examined, the regioisomers **4** and **4'** were provided in moderate yield with a 4/1 ratio. *N*-Boc pyrrolidine reacted smoothly to furnish the corresponding compound **5** in 31% yield. Moreover, tetrahydrothiophene provided the desired compound **6** under similar conditions in 30% yield. These results suggest that the weak C-H bonds adjacent to heteroatoms in the five-membered heterocycles could be directly functionalized with acetylene using our system. However, the less reactive cyclopentane (a five-membered carbocycle) could not serve as the hydrogen donor to provide the desired product **7**. In addition to five-membered heterocycles, we also examined the feasibility of

other heterocycles with different ring sizes (Fig. 4b). The experiments showed that the three-membered cyclic ether, 1,2-epoxypropane, could not be glued with acetylene to the carbonyl group for the formation of **8** or **8'**, which might be attributed to the epoxides easily opened ring. To our delight, the four-membered cyclic ether, oxetane, was successfully connected with acetylene, furnishing the desired ketone **9** in 26% yield, accompanied by 19% yield of **2a**. As shown in Fig. 3, THF, a five-membered cyclic ether, gave a good result with 69% yield of **3ae**. When the ring size was further increased from five to six, the corresponding ketone **10** tethering with tetrahydropyran (six-membered cyclic ether) could be isolated as well, but with a lower yield (17%). However, no desired product **11** could be detected when the seven-membered cyclic ether, oxepane, was used as the substrate. It seems that the larger membered heterocycles (over six members) are not suitable partners. Linear ether (isopropyl ether) failed to provide the desired product **12**, which is in line with the trend demonstrated in Fig. 4b. Interestingly, connecting 1,3-dioxolane with the carbonyl group was possible, giving regioisomers **13** and **13'** in a reasonable yield with a 5/1 ratio (Fig. 4c). The observed regioselectivity of H-abstraction in 1,3-dioxolane may be attributed to the anomeric lowering of the C-H BDE⁵⁹ (BDE _{α (C-H)} = 86.8 Kcal/mol vs BDE _{β (C-H)} = 88.2 Kcal/mol⁶⁰). After deprotection, 1,4-ketoaldehyde **14** was obtained efficiently from the crude regioisomers. Similar regioisomers **15**

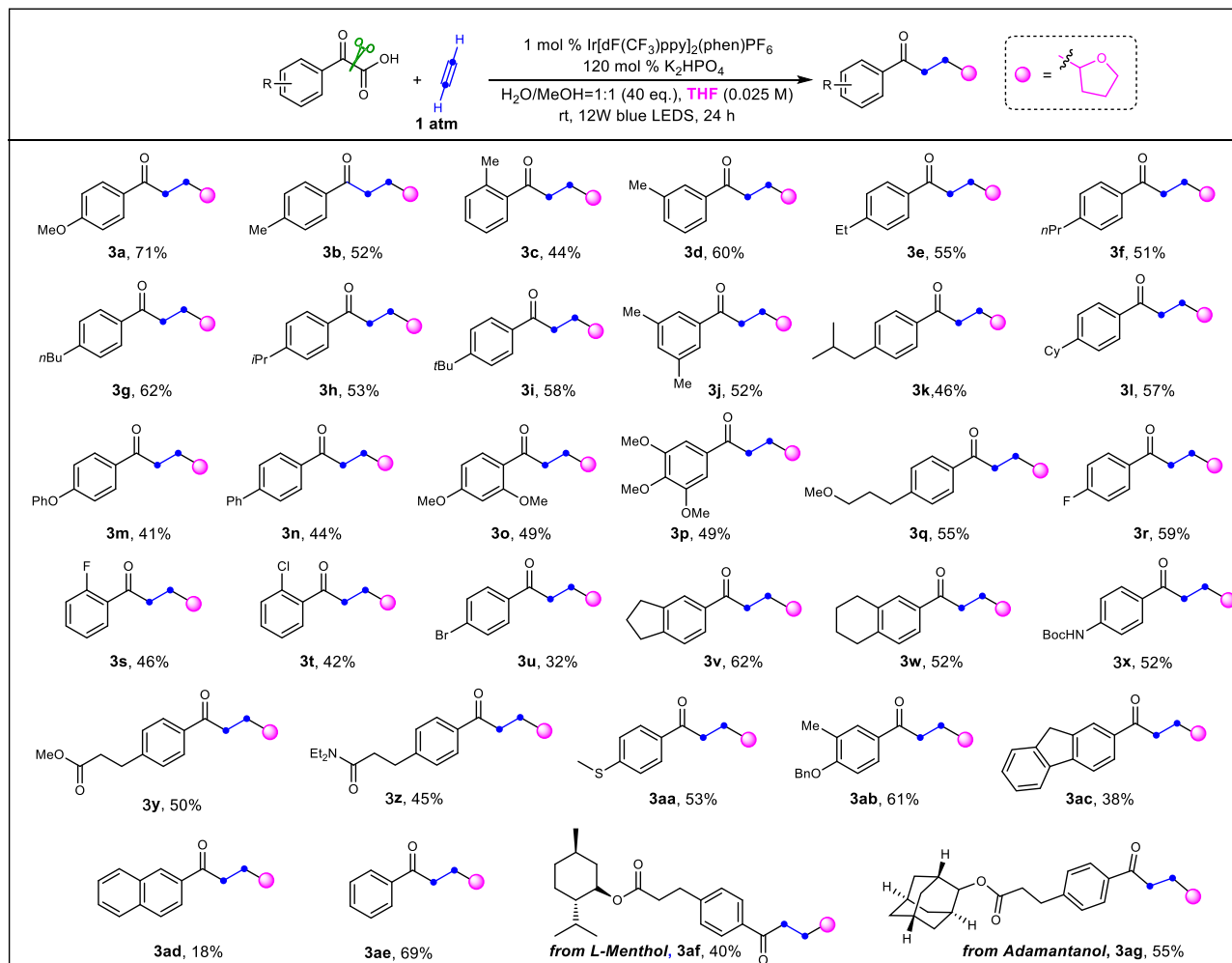


Fig. 3 Substrate scope for synthesis of tetrahydrofuran-containing molecules with acetylene. Standard conditions: α -Oxocarboxylic Acid (0.3 mmol), Ir[dF(CF₃)ppy]₂(Phen)PF₆ (0.01 equiv.), H₂O (20 equiv.), MeOH (20 equiv.) in a solution of THF (0.025 M) under the irradiation of blue LEDs under acetylene gas balloon for 24 h at room temperature. Isolated yield of products. dF(CF₃)ppy, 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl; phen, o-Phenanthroline; THF, tetrahydrofuran.

and **15'**, which are an ideal precursor of unsymmetric 1,4-diketones, were also obtained by switching from 1,3-dioxolane to 2-methyl-1,3-dioxolane. These outcomes illustrate that unsymmetric 1,4-dicarbonyl compounds could be accessed by using acetylene as a carbon glue, which greatly expands the synthetic scope of 1,4-dicarbonyl compounds. Compared to Knowles' strategy⁵⁶, our protocol utilized the vinyl radical generated in situ, to activate the weak Csp³-H bond of heterocycles avoiding the need for the additional abstractor and the preparation of the corresponding vinyl ketones as substrates. Our strategy provides alternative access to this type of compound from abundant feedstock under mild conditions.

To illustrate the synthetic utility of our strategy, a series of experiments were conducted (Fig. 5). On a preparative scale, 1,4-diketone **2q** was isolated in 60% yield, which was slightly higher than that of the 0.3 mmol scale, suggesting that large-scale production might be feasible. Synthesis of enantiomerically enriched Ombitasvir **19**³³, an orally bioavailable and potent inhibitor, was achieved using chiral **18** which was prepared in 4 steps from **2q** via sequential asymmetric reduction, methanesulfonation, nucleophilic cyclization³³ and coupling steps (73% yield for 4 steps, *dr* 5/1) (Fig. 5a). Moreover, simple transformations of the 1,4-dicarbonyl moiety afforded a range of synthetically useful scaffolds (Fig. 5b). For instance, heterocyclic

molecules, such as substituted furan **20**, substituted thiophene **21** and substituted pyrroles **22–23** were obtained via the cyclization of **2a** under acidic condition or in the presence of Lawesson's reagent, ammonium acetate or benzylamine. The 1,4-dicarbonyl compound was easily transformed to naphthalene-2,3-diylbis(phenylmethanone) **24** in 98% yield under basic conditions with *o*-phthalaldehyde. Additionally, alkene **25** was accessed through a Wittig reaction with methyltriphenylphosphonium bromide. The derived 1,3-butadiene **26** was also obtained through a sequential reduction and elimination processes. Furthermore, the 1,4-dicarbonyl compound **2a** was transformed to cyclobutene **27** in good yield according to the known literature⁶¹.

Mechanistic studies. To further gain mechanistic insights, control experiments were performed (Fig. 6). In the presence of the radical trap TEMPO, the reaction completely shut down (Fig. 6a, top), indicating that a radical intermediate might be involved in this transformation. The reaction of **1a** was performed for 2 h under standard conditions, affording **2a** in 24% yield (Fig. 6a, bottom). Additionally, no change in the yield of **2a** was observed when the same reaction was conducted for 2 h and then for an additional 22 h without light (Fig. 6a, bottom). These experiments indicate that the reaction is a visible-light photocatalysis process. Considering benzaldehyde was detected as a by-product during the reaction

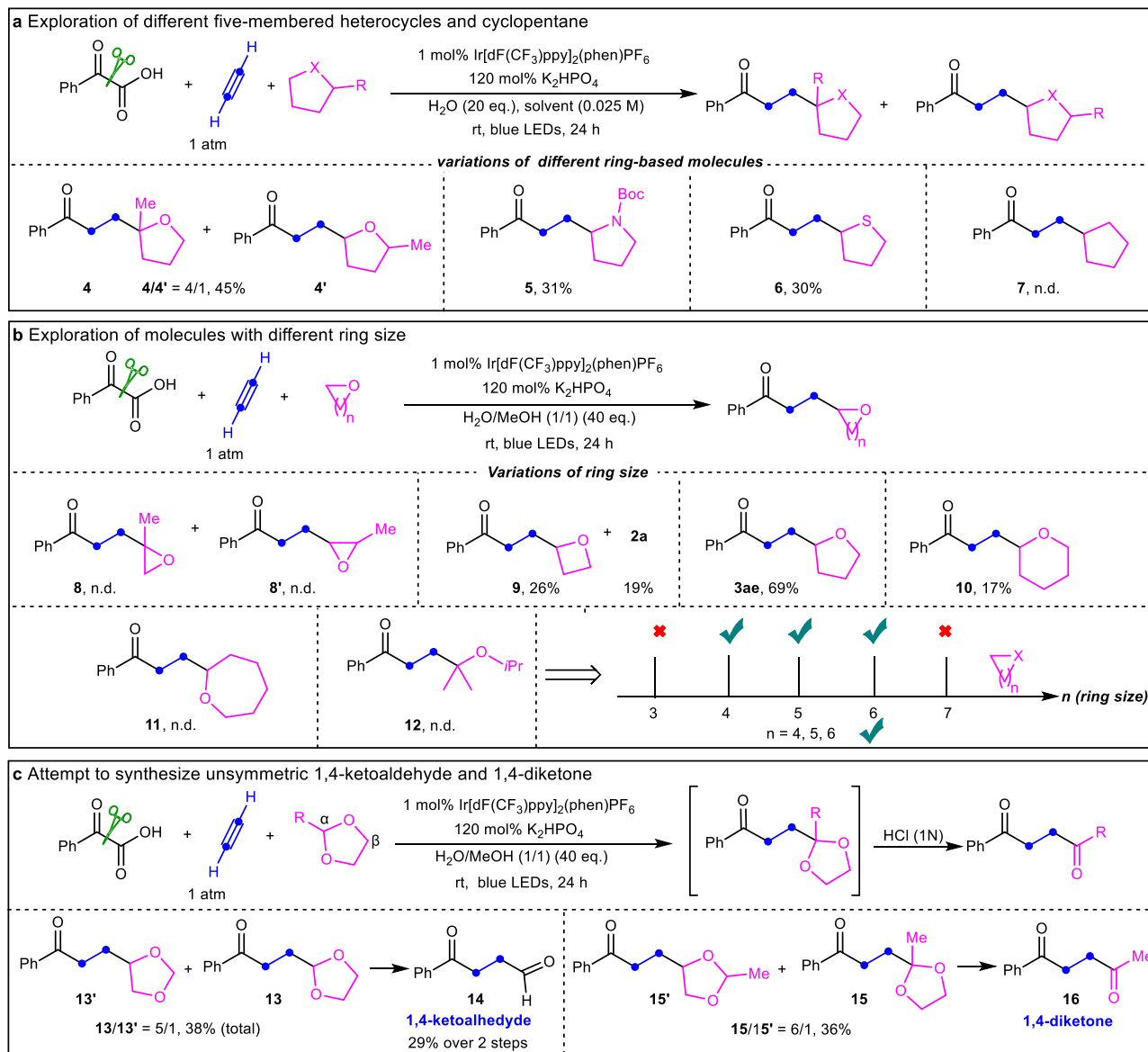


Fig. 4 Exploration of different cyclic molecules with acetylene. **a** Exploration of different five-membered heterocycles and cyclopentane. 2-Me-THF was used as solvent for **4** and **4'**. *N*-Boc pyrrolidine (5 equivalent) and 1,2-dichloroethane (solvent) were used for **5**. Tetrahydrothiophene (5 equivalent) and acetonitrile (solvent) were used for **6**. Cyclopentane was used as solvent for **7**. dF(CF₃)ppy, 3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridinyl]phenyl; phen, *o*-Phenanthroline; DCE, 1,2-Dichloroethane; eq, equivalent; 2-Me THF, 2-Methyltetrahydrofuran. **b** Exploration of molecules with different ring size. All the heterocycles were used as solvent or cosolvent, see supplementary information for details. **c** Attempt to synthesize unsymmetric 1,4-ketoaldehyde and 1,4-diketone. The heterocycles were used as solvent.

condition optimizations, we explored the reaction of **1d** and benzaldehyde under the standard conditions (Fig. 6b, top) to verify whether benzaldehyde was the reaction intermediate. No cross-over product **28** was observed, strongly suggesting that benzaldehyde is not likely an intermediate of this transformation. According to our initial assumption and the inherent reactivity of the vinyl radical, direct abstraction of a hydrogen atom from hydrogen donors to produce the vinyl phenyl ketone is reasonable. As a result, the reaction of stoichiometric vinyl phenyl ketone **29** and 2-(4-methylphenyl)-2-oxoacetic acid **1d** was performed under the standard conditions without acetylene, affording the expected product **28** in 26% yield (Fig. 6b, bottom). The result showed that the corresponding vinyl phenyl ketone is the key intermediate in our system. To get further insight into the hydrogen source, chloroform-*d* was used as the solvent instead of dichloromethane in the reaction of vinyl phenyl ketone **29** and 2-(4-methylphenyl)-2-oxoacetic acid

1d (Fig. 6c, top) and furnished **28** in 64% yield with 0% D-incorporation in the α -position of the carbonyl group according to ¹H NMR analysis. In sharp contrast to this phenomenon, > 90% D was incorporated into the molecule **30a** when dichloromethane-*d*₂ was used in the model reaction (Fig. 6c, entry 1), indicating one of the hydrogens next to the carbonyl group comes from the solvent. When the corresponding potassium salt of benzoylformic acid **1aa** was tested under the standard conditions using dichloromethane-*d*₂ as the solvent and D₂O as an additive, the corresponding product **31a** bearing > 90% D-incorporation in each methylene site was isolated without **30a** being detected (Fig. 6c, entry 2). Additionally, > 90% D-incorporation was verified in one of the methylene sites using D₂O as the additive (Fig. 6c, entry 3), meaning another hydrogen adjacent to the carbonyl group originates from water. To further exclude that the deuterated product was generated from **2a** under standard conditions through H/D exchange with D₂O, **2a** was

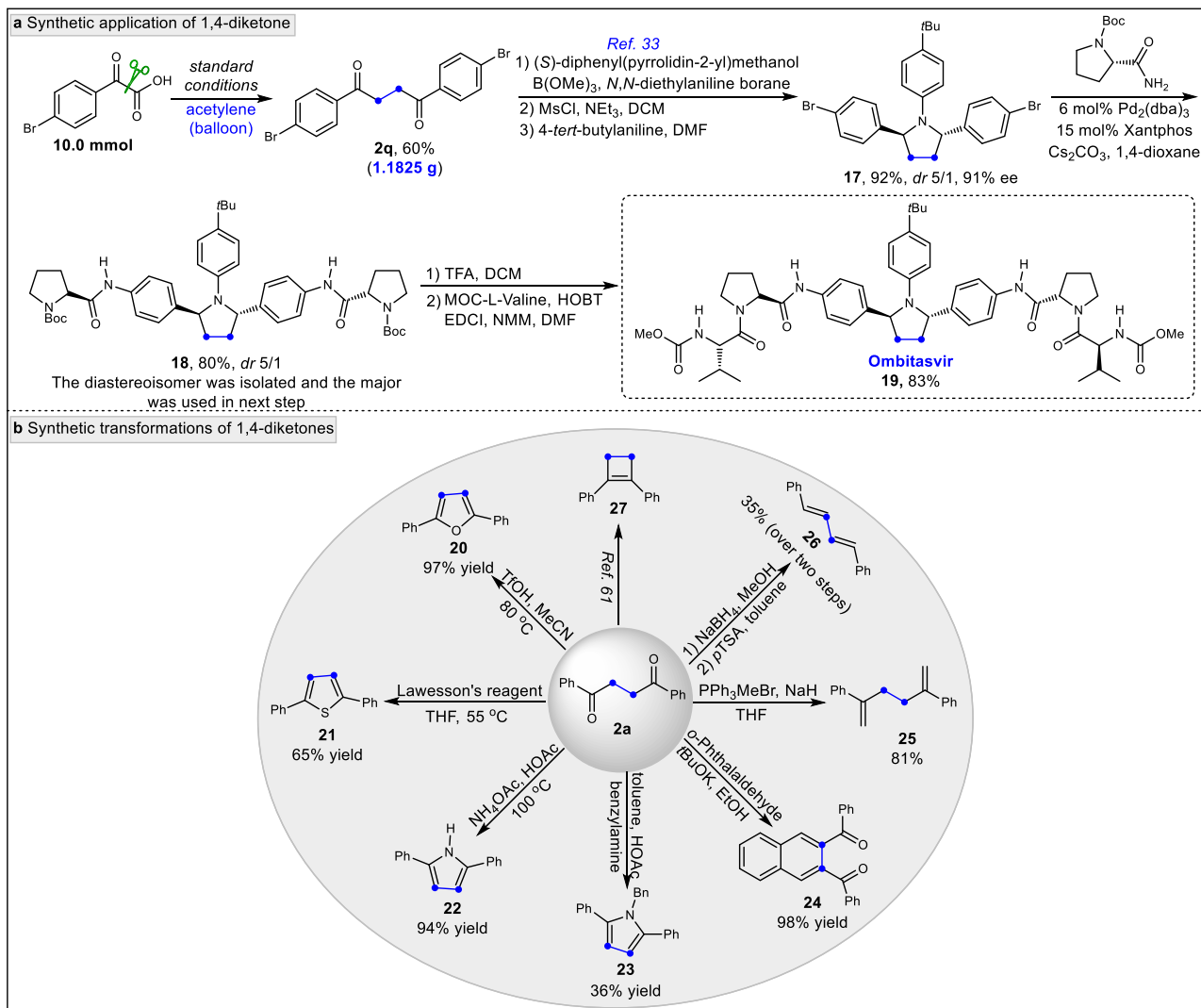


Fig. 5 Application potentials in the syntheses of bioactive molecules and transformations. **a** The 1,4-diketone **2q** could be prepared in gram-scale with no decrease in isolated yield. The approved drug Ombitasvir could be efficiently constructed with our strategy. DCM, Dichloromethane. MsCl, Methanesulfonyl chloride. DMF, *N,N*-Dimethylformamide. TFA, Trifluoroacetic acid. HOBT, 1-Hydroxybenzotriazole hydrate. EDCI, *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride. NMM, *N*-methylmorpholine. **b** diverse high-valued compounds could be prepared from 1,4-diketone **2a**.

subjected to reaction conditions with D_2O instead of H_2O (Figure 6c, entry 4). Interestingly, no deuterated products **30a** or **31a** were found with the 96% recovery of **2a**. This experiment suggested that the CH_2 of **2a** cannot be deuterated through H/D exchange with D_2O under standard conditions. Taken together, these results demonstrated the water and solvent are both hydrogen sources but used in the different stages of the reaction process. This is further supported by the mechanistic experiments for **3ae** (see Supplementary Fig. 6 and Supplementary Fig. 7).

Mechanistic proposal. Based on the previously reported literature^{54,55,62–66} and the aforementioned mechanistic studies, a plausible mechanism for this transformation is proposed in Fig. 7. Upon irradiation with visible light, the photocatalyst $Ir[dF(CF_3)ppy]_2(phen)PF_6$ **I** is known to access the highly oxidizing excited state (ES) species **II** ($[Ir^{3+}]^*$). Which could be reductively quenched by the anion of α -oxocarboxylic acid **1** to generate an acyl radical **32**^{62,65} through a decarboxylative pathway, and the reduced species **III**. The generated **32** could be captured by acetylene gas to afford vinyl radical species **33** which is highly

unstable and quickly abstracts a hydrogen from dichloromethane to provide the electron-deficient vinyl ketone **34** accompanied by the generation of **35**. This proposed process is in line with the fact that the BDE of the Csp^2-H bond (~ 110 kcal/mol)^{54,55} exceeds that of Csp^3-H bond of dichloromethane (~ 95 Kcal/mol)⁶⁶. The reduced species **III** could be oxidized to regenerate the photocatalyst **I** by **35**, furnishing the carbon anion **36** which could be protonated to regenerate dichloromethane. Subsequently a Giese radical addition reaction occurs with another molecule of acyl radical **32**, which adds quickly to alkene **34** to produce a new carbon radical **37**. Then a single-electron reduction of radical **37** by **III** affords the carbon anion **38** and regenerates the photocatalyst **I**. The desired product is obtained after protonation of **38**. The phenomenon that nearly no electron-deficient alkene **34** was observed could be attributed to the fact that **34** is more highly reactive than the parent acetylene. Similarly, vinyl radical species **33** could also abstract hydrogen from heterocycles bearing weaker C-H bonds, affording alkene **34** and nucleophilic radical intermediate **39** which is rapidly captured by **34** to produce **40**. Then the sequential single electron transfer (SET)/protonation process

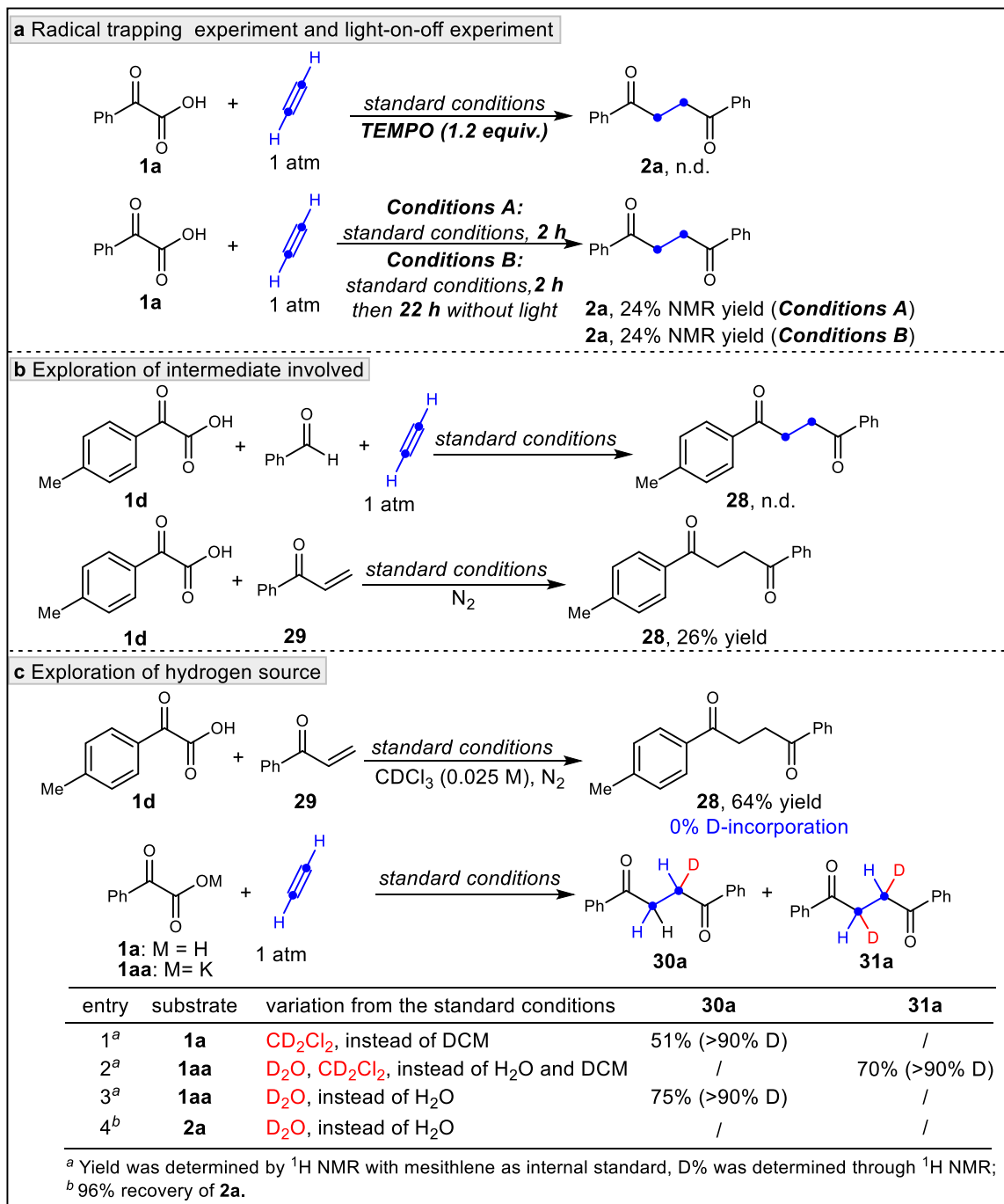


Fig. 6 Mechanistic studies. **a** Radical trapping and light-on-off experiment were performed, suggesting this transformation might proceed via a radical pathway. TEMPO, 2,2,6,6-tetramethylpiperidinoxy. **b** Exploration of intermediate involved. n.d., not detected. **c** Exploration of hydrogen source. Both the solvent and water are the hydrogen source of this transformation. DCM, Dichloromethane.

occurs to provide the final product 3. It is noteworthy that dichloromethane functions as solvent, as hydrogen donor, and as oxidant precursor to facilitate the regeneration of the reduced photocatalyst. In addition to serving as hydrogen donors and solvents (special conditions), heterocycles also work as the nucleophilic components due to the higher nucleophilicity of their corresponding radicals over that of 35.

In summary, a diverse synthesis protocol for C2-linked functionalized molecules with gaseous acetylene was developed, which provided an efficient method to quickly access a variety of compounds through connecting two components together via a molecular glue strategy with readily available substrates and

abundant acetylene gas under mild conditions. A series of 1,4-diketones, which are important precursors of an array of heterocycles, were quickly constructed. Importantly, the reaction system was expanded to construct heterocycle-containing compounds. These compounds form when the intermediate vinyl ketone is intercepted by a radical intermediate formed from a heterocycle C-H abstraction. In both of these transformations, acetylene is incorporated in the final product as a CH₂-CH₂ bridge. Additionally, mechanistic studies demonstrated that one of the formed C-H bonds is created via a C-H abstraction from the hydrogen donor, such as dichloromethane or a heterocycle, and the other via protonation from water or methanol. Moreover,

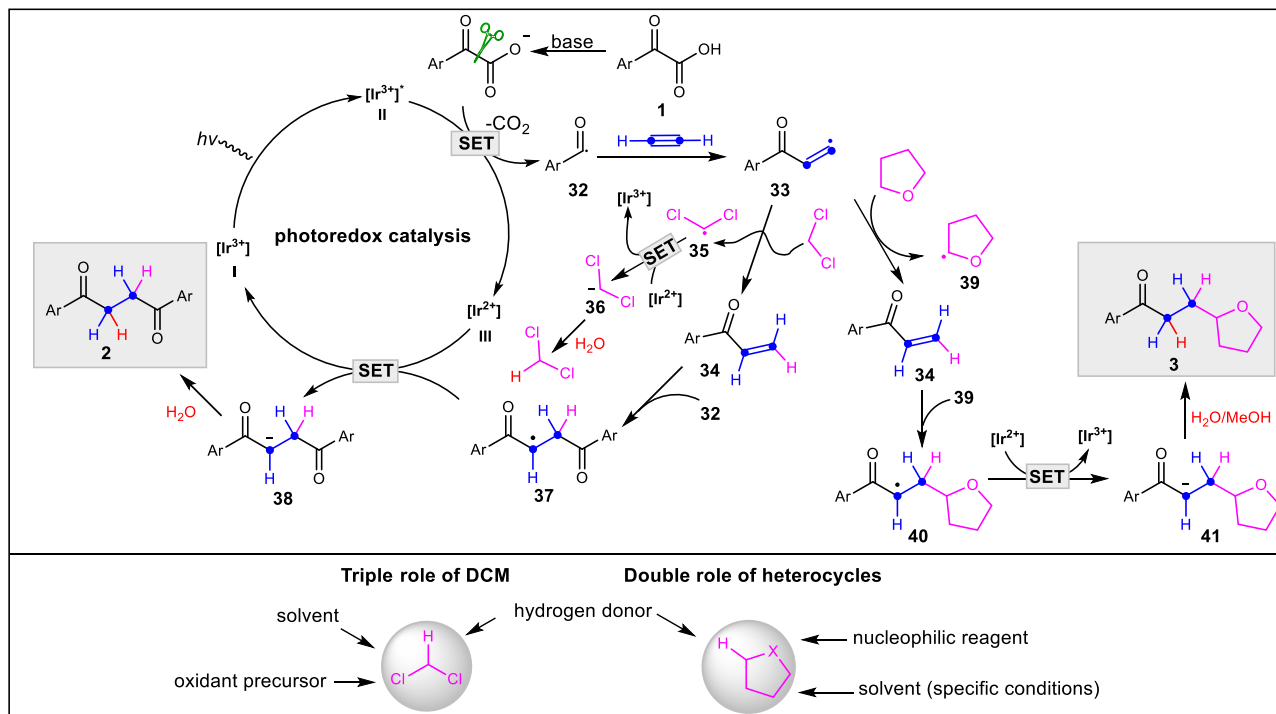


Fig. 7 A plausible mechanism. The catalytic cycle begins with oxidative single electron transfer (SET), generating the acyl radical **32**. The intermediate then undergoes addition to acetylene to generate vinyl radical **33**. Intermolecular hydrogen atom transfer (HAT) then occurs to afford aryl vinyl ketone **34** accompanied by the generation of **35** or **39**. At last, the Giese radical reaction between aryl vinyl ketone and another acyl radical **32** or **39** occur to furnish the final product.

this approach provides ready access to interesting, functionalized molecules and expands the utility of acetylene in organic synthesis, which will inspire new perspectives for value-added chemical synthesis using acetylene and promote the renaissance of catalytic transformations for acetylene.

HRMS data and NMR spectra are available within the article and the Supplementary Information.

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Methods

Materials. Unless otherwise noted, all the materials were obtained commercially and used without further purification. All the solvents were treated according to general methods. Flash column chromatography was performed over silica gel (300–400 mesh). See Supplementary Methods for experimental details.

General procedure A for the synthesis of 1,4-dicarbonyl compounds. To an oven-dried 25 mL flask, Ir[dF(CF₃)ppy]₂(phen)PF₆ (0.003 mmol), 2-aryl-2-oxocarboxylic acid (0.3 mmol), K₂HPO₄ (0.36 mmol), H₂O (20 equiv.) and DCM (12 mL) were added sequentially under N₂. The flask was degassed through three freeze-pump-thaw cycles under acetylene and then an acetylene gas balloon was attached through a long syringe needle. The reaction mixture was irradiated by 12 W blue LEDs at a distance of 5 cm for 24 h at room temperature. The reaction mixture was filtered through a short pad of silica using ethyl acetate. The filtrate was concentrated *in vacuo* before it was purified by flash chromatography on silica gel to afford the desired product.

General procedure B for the synthesis of heterocycle-containing compounds. To an oven-dried 25 mL flask, Ir[dF(CF₃)ppy]₂(phen)PF₆ (0.003 mmol), 2-aryl-2-oxocarboxylic acid (0.3 mmol), K₂HPO₄ (0.36 mmol), H₂O/MeOH (1/1, 40 equiv.) and THF (12 mL) were added sequentially under N₂. The flask was degassed through three freeze-pump-thaw cycles under acetylene and then an acetylene gas balloon was attached through a long syringe needle. The reaction mixture was irradiated by 12 W blue LEDs at a distance of 5 cm for 24 h at room temperature. The reaction mixture was filtered through a short pad of silica using ethyl acetate. The filtrate was concentrated *in vacuo* before it was purified by flash chromatography on silica gel to afford the desired product.

Data availability

The authors declare that data relating to the characterization of materials and products, general methods, optimization studies, experimental procedures, mechanistic studies,

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Author contributions

B.Y. and S.Z. designed the experiments. B.Y. performed experiments. S.L. synthesized the substrates. S.Z. and Y.W. codirected the synthetic applications of this method. B.Y. wrote the paper and S.Z. revised-reviewed & edited the paper. All authors discussed the results and commented on the manuscript. S.Z. directed the whole project.

Competing interests

The authors declare no competing interests.

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Hydrogen radical-shuttle (HRS)-enabled photoredox synthesis of indanones via decarboxylative annulation

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Hydrogen atom transfer (HAT) process is a powerful and effective strategy for activating C-H bonds followed by further functionalization. Intramolecular 1,n (n = 5 or 6)-HATs are common and frequently encountered in organic synthesis. However, intramolecular 1,n (n = 2 or 3)-HAT is very challenging due to slow kinetics. Compared to proton-shuttle process, which is well established for organic synthesis, hydrogen radical-shuttle (HRS) is unexplored. In this work, a HRS-enabled decarboxylative annulation of carbonyl compounds via photoredox catalysis for the synthesis of indanones is developed. This protocol features broad substrate scope, excellent functional group tolerance, internal hydrogen radical transfer, atom- and step-economy. Critical to the success of this process is the introduction of water, acting as both HRS and hydrogen source, which was demonstrated by mechanistic experiments and density functional theory (DFT) calculations. Importantly, this mechanistically distinctive HAT provides a complement to that of typical proton-shuttle-promoted, representing a breakthrough in hydrogen radical transfer, especially in the inherently challenging 1,2- or 1,3-HAT.

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As a powerful and effective strategy, hydrogen atom transfer (HAT) catalysis has been demonstrated as an ideal platform for C–H bonds functionalizations, majorly involving proton shift and hydrogen radical transfer^{1–12}. When it comes to proton transfer, proton-shuttle (PS) catalysis has been well developed for the past decades, providing a highly efficient strategy for C–H functionalization, especially in transition-metal-catalyzed C–H activation^{13–15} and insertion of carbenes into heteroatom–hydrogen bonds^{16–24} (Fig. 1a). It has been recognized that PS catalysts, such as water¹⁶, acid^{13, 17–23} and alcohol²⁴, could lower the reaction barrier by forming cyclic molecular complexes that involve lower ring strain and facilitate intra- or intermolecular HAT. In the latter process (hydrogen radical transfer), a reactive radical species, traditionally, was needed to abstract hydrogen from C–H bond to generate the corresponding carbon-centered radical intermediate^{6–8, 11, 25–28}, triggering the following functionalization process. Based on the great achievements in PS catalysis, we wondered whether a similar hydrogen radical-shuttle (HRS) strategy could be used to complete the HAT process (Fig. 1b). Notably, the core difference between HRS-promoted HAT and that of polarity-reversal-catalyzed^{29, 30} is that hydrogen radical transfer occurs from a neutral position to another non-radical site. To the best of our knowledge, no successful examples utilizing this strategy have been reported. Importantly, this would be another complementary process to that of PS catalysis. With this HRS strategy in mind, we engaged to develop practical approaches for important scaffolds synthesis via a radical pathway.

Considering the prevalence of indanones and their derivatives in pharmaceuticals and biologically active natural products^{31–35}, a lot of efforts have been devoted to developing effective strategies for indanones synthesis^{36–40}. Traditionally, indanones were prepared from the corresponding indenols or indenones. Among a variety of approaches, transition-metal catalyzed annulation of *ortho*-halogenated carbonyl compounds and alkynes is one of the highly efficient and general strategies to construct indenone scaffolds^{41–45}. For example, Yamamoto⁴⁶ and Cheng^{47, 48} reported the cyclization of *ortho*-halogenated carbonyl compounds and alkynes to construct indenols, respectively. Kong⁴⁹ reported the indanones synthesis based on hydrogen auto-transfer strategy through nickel catalysis. Notwithstanding great achievements that have been made, these methods typically suffered from the prefunctionalization of the corresponding starting materials. Direct C–H bond functionalization to access indenones through Rh-catalyzed procedures has also been developed^{50–52}. However, among these traditional strategies, a stepwise process has to be adopted because additional oxidation and/or reduction processes are often required when converting the indenols or indenones to indanones (Fig. 1c). Therefore, developing a direct C–H annulation of carbonyl compounds with alkynes for indanones synthesis in one step is highly appealing and desirable.

Recently, aryl *Csp*²–H functionalization involving a radical process has emerged as an ideal and powerful strategy to construct C–C bonds, along with diminished cost and waste^{53, 54}. These methods rely on certain carbon radicals trapped by arenes and followed by the aromatization process, which might provide

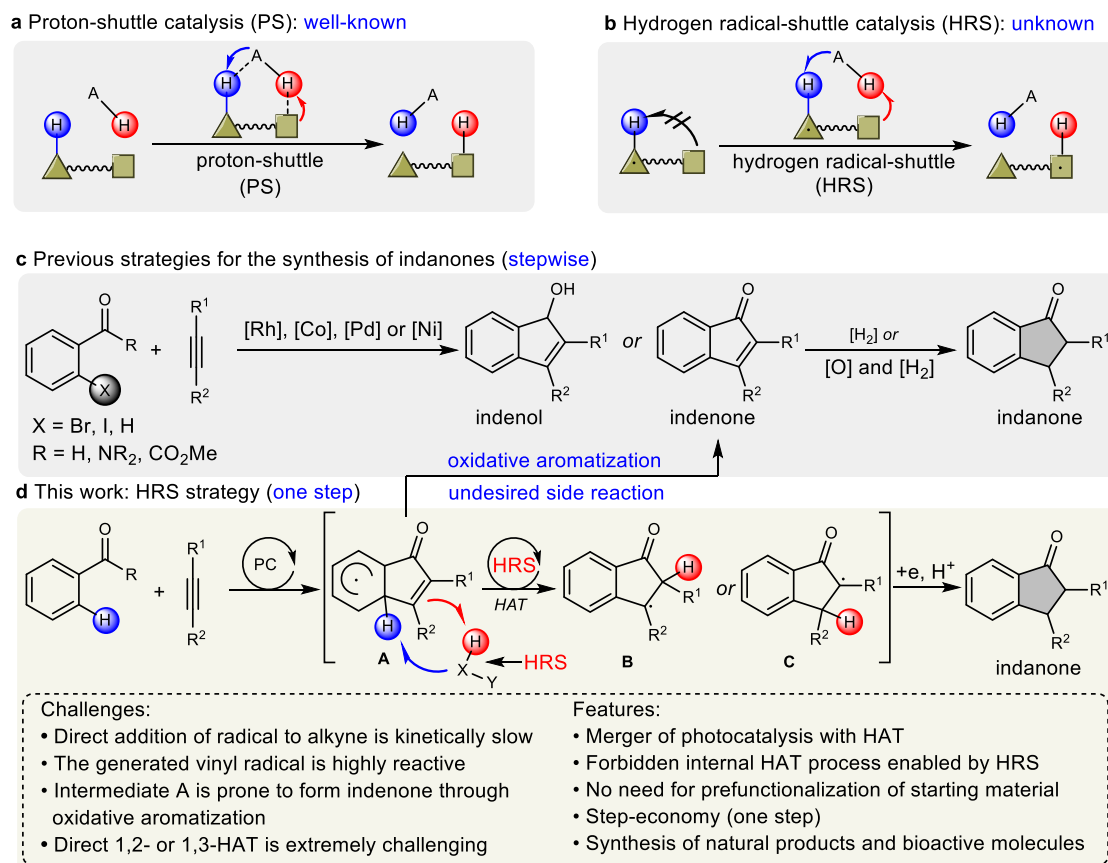


Fig. 1 Proton/hydrogen radical-shuttle catalysis and indanone scaffold synthetic strategy. **a** Proton-shuttle catalysis model. **b** Hydrogen radical-shuttle catalysis model. **c** Traditional synthetic strategies for indanones by annulation reaction of alkynes. **d** HRS-enabled strategy for indanone synthesis (this work). PC photocatalyst.

an alternative protocol for the direct annulation of carbonyl compounds to construct indanones. In addition, acyl radicals produced efficiently from α -oxocarboxylic acid, aldehyde, acyl halide, and so on via radical pathway⁵⁵, have been well researched with alkenes. Inspired by these developments, we anticipated that if we could utilize the electron-deficient vinyl radicals, generated from acyl radical addition to alkynes, to achieve direct construction of indanones through the dearomatic radical intermediate **A**. However, the typical oxidative aromatization strategy from intermediate **A** to the desired indanone product is often problematic due to (i) the electron-deficient indenone is readily prone to [2 + 2] cycloaddition under photoredox conditions⁵⁶ and (ii) the Giese-type reaction of acyl radical with indenone would be the main side reaction⁵⁷. Moreover, the following external reduction steps were also required from indenone to indanone. To overcome these obstacles, we questioned if it is possible to merge HAT with single electron transfer (SET), resulting in the generation of intermediate **B** or **C**. We recognized that such a merger might realize rearomatization of intermediate **A** and avoid the generation of indenone, providing an aromatization model and an ideal strategy for the direct construction of indanones without additional prefunctionalization of substrates and external steps. However, the direct addition of radicals to unactivated alkynes is kinetically slow^{58, 59} and the generation of corresponding high-energy vinyl radical intermediate is highly reactive, which can participate in various undesirable open-shell pathways. In addition, intermediate **A** is prone to form indenone through oxidation/elimination steps. More importantly, as the critical problem in our design, the HAT (1,2- or 1,3-HAT) strategy forming **B** or **C** is challenging^{11, 60, 61} due to the high activation energy, which could be attributed to the increased C–H–C/heteroatom strain. According to the analysis above, an HRS-enabled HAT strategy, we speculated, might be an ideal protocol to circumvent this problem (Fig. 1d). A suitable HRS catalyst was required to modulate the reactivity of intermediate **A**, thereby providing an opportunity for rearomatization and hydrogen radical transfer of **A** simultaneously, furnishing the effective synthesis of indanones.

In this work, we report an HRS-enabled decarboxylative annulation of carbonyl compounds for the synthesis of indanones via photocatalysis with excellent functional group tolerance, broad substrate scope as well as an atom- and step-economy. The key to the success of this protocol is the application of water molecules, functioning as both solvent and HRS and promoting the hydrogen radical transfer in formal 1,3-HAT process, which was demonstrated by mechanistic experiments and DFT calculations.

Results and discussion

Reaction development. From a design perspective, with benzoylformic acid **1** as acyl radical precursor, we envisioned that this HRS-promoted HAT/SET strategy could be outlined as Fig. 2a. Irradiation of photocatalyst **PC** (**I**) with visible light generates the long-lived excited state **II**, which is a strong oxidant, capable of oxidizing **2** to form a nucleophilic acyl radical **3**⁵⁷ and a reduced state **III**. Meanwhile, the alkyne **4** reacts readily with acyl radical **3** to form the vinyl radical **5**. The open-shell radical **5** is expected to rapidly engage in addition to the aryl ring, generating the dearomatic radical **6**. At this stage, we hoped that this radical species **6** would undergo the critical hydrogen radical transfer step to generate key intermediate **7** or **7'** assisted by HRS. Single-electron reduction of radical **7** or **7'** by **III** to afford carbon anion **8** or **8'**, followed by protonation to afford the indanone **9**.

Our initial efforts sought to evaluate different potential HRSs which are effective for the direct assemble of indanones with

potassium 2-oxo-2-phenylacetate **10** and phenylacetylene **4** as model substrates, along with $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$ as the photocatalyst under N_2 with illumination by blue LEDs. After a series of explorations on several potential HRS catalysts (H_2O , MeOH , EtOH , and acetic acid), to our delight, 22% yield of indanone was isolated with water as an additive (Fig. 2b). A trace amount of desired indanone **9** was detected without water.

Further screening of the reaction conditions using benzoylformic acid **1** and phenylacetylene **4** as model substrates found that the indanone **9** could be isolated in 86% yield using $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$ as the photocatalyst and water as HRS under N_2 with illumination by blue LEDs at 100 °C (Fig. 2c). Control experiments revealed that the photocatalyst, visible light, and water were all essential components for achieving the high efficiency of this reaction (see Supplementary information for details).

Substrate scope investigation. With the optimized conditions in hand, we next evaluated the variations of 2-oxo-2-arylacetic acids and alkynes that are applicable to the developed reaction (Fig. 3). With respect to the 2-oxo-2-arylacetic acid partner, we observed moderate to excellent yields of the desired products (**11**–**31**) with a wide range of substrates bearing different substituents. The methyl groups at the *ortho*-, *meta*-, and *para*-positions on the phenyl ring of 2-oxo-2-arylacetic acid could be tolerated (**11**–**13**). With respect to the *meta*-substituted 2-oxo-2-phenylacetic acid, regioisomers **12** and **12'** were obtained with 0.75/1 *rr*. A range of 2-oxo-2-phenylacetic acids bearing both the electron-donating and electron-withdrawing substituents on the phenyl ring, no matter for 1°-, 2°-, 3°-alkyl substituents or linear, cyclic substituents, were amenable substrates (**14**–**24**). The strong electron-withdrawing substituents decrease the conversion and yields. This observation may be ascribed to the reduced reductive quenching ability toward photoexcited $[\text{Ir}]^*$. The sp^2 -hybridized phenyl-substituted 2-oxo-2-phenylacetic acid underwent smoothly to give a 65% yield of indanones (**25**). Notably, 2-oxo-2-phenylacetic acid with additional functionalities was also compatible with this protocol. For example, various functional groups, such as ether, halides, trifluoromethyl, easily-oxidized thioether, ester, and amide remain intact to furnish the corresponding products (**26**–**29**). In addition to substituted 2-oxo-2-phenylacetic acid-type substrate, 2-(naphthalen-2-yl)-2-oxoacetic acid could also be successfully converted into the desired product **30** in reasonable yield. Interestingly, **31** and **31'** could be obtained in 83% yield with region-selectivity (*rr* 1/2) from the corresponding substrates. Having established that this transformation tolerates various 2-oxo-2-arylacetic acid substrates, we then turned our attention towards evaluating the scope of the alkyne components. For the simple aromatic alkynes with alkyl or phenyl substituents, the corresponding products (**32**–**37**) were isolated in 43–84% yields. Evaluation of a series of alkynes that contained various functional groups, such as fluoro, chloro, bromo, nitrile, aldehyde, ketone, ester, acid, phenol, free amine and alcohol, provided indanones **38**–**48** in 43–85% yield, potentially allowing for the subsequent orthogonal functionalization. Notably, alkynes with synthetic handles, such as halides (**38**–**40**) and boronic ester **49**, were readily incorporated into the accessible indanone scaffolds, which highlights their potential applications for the incorporation of these scaffolds into more complex targets. Additionally, the developed protocol was also tolerant of the alkyne containing easily oxidized thioether, as demonstrated by **50**, which was isolated in 63% yield. Considering that heteroaryl-substituted compounds are highly desirable building blocks in drug discovery, we also evaluated a range of heteroaryl-substituted alkynes that would provide access to heteroaryl-substituted

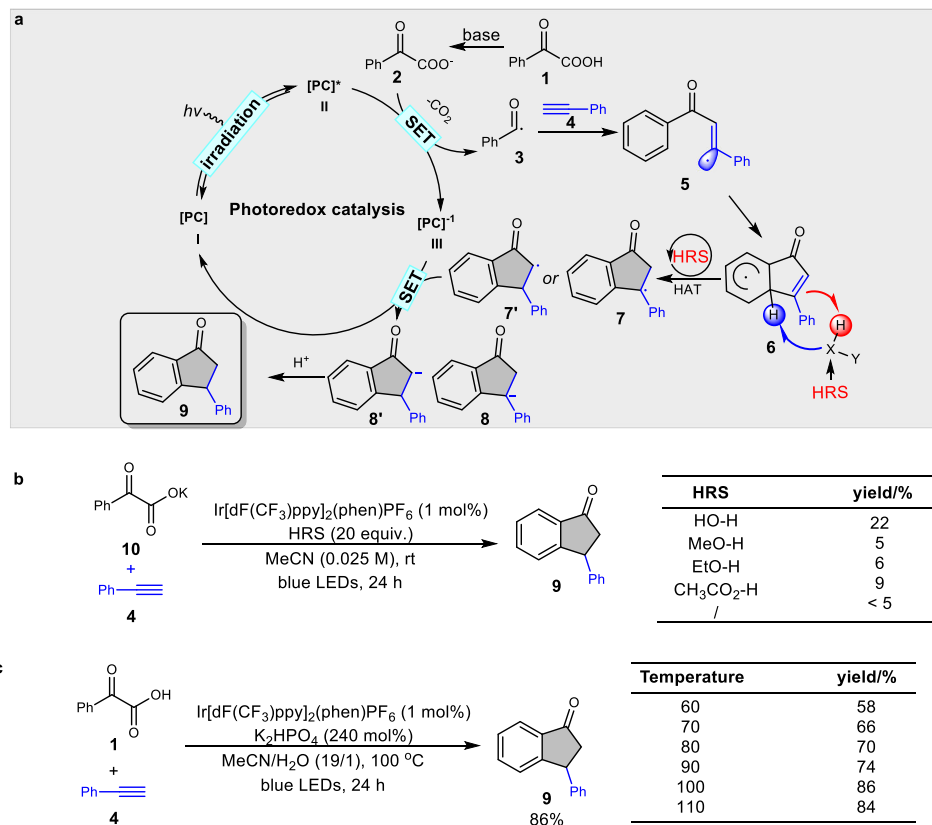


Fig. 2 Reaction development. **a** Proposed mechanism for synthesis of indanone. **b** Evaluation of possible HRS catalyst. **c** Investigation of temperature's effect on the reaction. PC photocatalyst, HRS hydrogen radical-shuttle.

indanones. Although these scaffolds traditionally required multistep syntheses, the developed protocol allows for the construction of heteroaryl-substituted indanones in a single step from readily available precursors. For example, a wide range of five- and six-membered heteroaryl alkynes, such as benzofuran, thiophene, indole, and pyridine-derived substrates were functionalized with high efficiency (**51–55**). When 2-naphthyl alkyne was subjected to the standard conditions, a reaction occurred to afford the desired product **56** in 69% yield. Of particular note is that when 1,4-diethynylbenzene was subjected to the standard conditions, mono-cyclization product **57** could be obtained in 20% yield, accompanied with an equal amount of dicyclization product **58**. Dicyclization product **58** could be selectively produced in 61% yield with 1.1/1 *dr* when an excess amount of acid partner was used. Moreover, tricyclization compound **59** could be obtained in one step under the same reaction conditions by using 1,3,5-triethynylbenzene as an alkyne component. To further explore the scope of this reaction, other kinds of alkynes were also tested. The silicon-substituted alkynes and methyl propiolate were also suitable substrates to provide the titled products (**60–61**). Besides the terminal alkynes, the internal alkynes, including aromatic alkynes and alkyl alkynes, could also be successfully transformed into 2,3-disubstituted indanones with diastereometric ratios ranging from 7.2/1 to 20/1 (**62–68**). We also evaluated 2-oxo-2-phenylacetic acids and aromatic alkynes both with electron-donating substituents under standard conditions, providing the corresponding products in 67–80% yield (**69–71**). Importantly, the reaction could be reproduced on a 6 mmol scale to provide gram quantities of **71** in an increased concentration. There was almost no change in the chemical yield, suggesting that large-scale chemical production might be possible. It is noteworthy that cyclic internal alkyne, cyclooctyne, could also be

transformed to the corresponding indanone **72** in 30% yield with 3.7/1 *dr*.

To explore its utility for late-stage functionalization of complex molecules, several natural products or bioactive molecules-derived alkynes were tested for this developed reaction system. As shown in Fig. 4, the estrone-derived alkyne could be efficiently transformed into the indanone **73** in a 65% yield. In addition, aryl alkyne with an ester-linked androstrone also participated in this transformation smoothly, furnishing **74** in 75% yield. Similarly, the corresponding alkyne derived from menthol and adamantanol were both suitable alkyne partners for this protocol, affording the desired products **75** and **76** in 85% and 77% yield, respectively. These results show great potential for the structural modification of an array of complex biological molecules in medicinal chemistry.

To further showcase the synthetic utility of this developed strategy, we next made efforts on the synthesis of indanone-containing natural products, biologically and pharmaceutically molecules. For example, the 3-substituted indanone-1-one **78**, prepared using this method in 63% yield, was the key intermediate in the synthesis of indatraline **79**⁶², an approved and antidepressant drug (Fig. 5a). Moreover, synthesis of PPAR γ agonist **84**⁶³ could be achieved via oxidated dehydrogenation of corresponding indanone **83**, which was prepared in three steps from α -oxocarboxylic acid **80** and **4** using our developed protocol, followed by dehalogenation and α -esterification (Fig. 5b). Importantly, pauciflorol F **87**⁶⁴ and isopauciflorol F **90**⁶⁵, both are natural products and bioactive molecules, could also be selectively assembled by using different alkynes and aryl halides (Fig. 5c and d).

With the indanone scaffolds in hand, further chemical transformations were also performed to demonstrate the potential

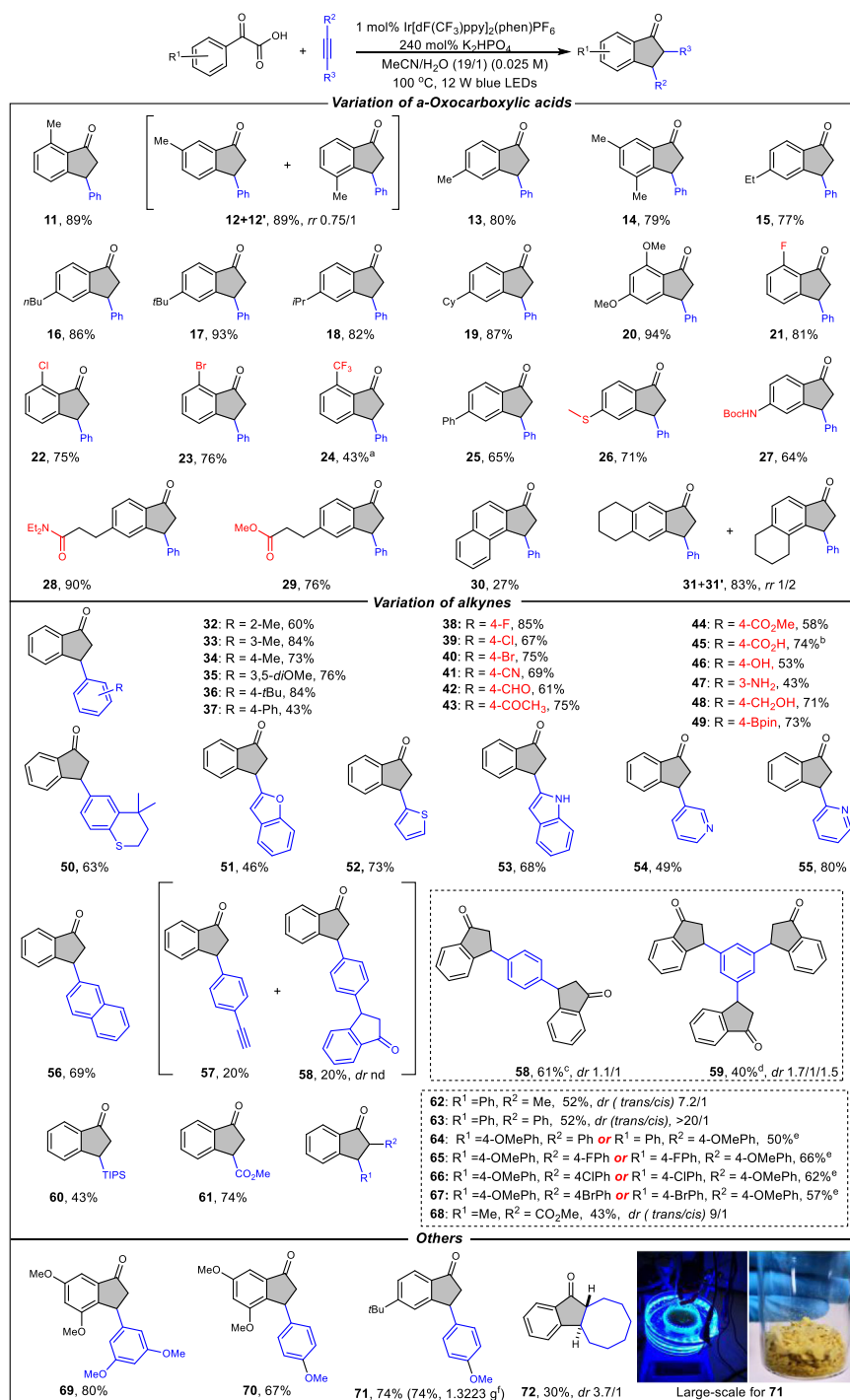


Fig. 3 Exploration of substrate scope. Reactions were performed with acid (1.0 mmol), alkyne (0.5 mmol), Ir[dF(CF₃)ppy]₂(phen)PF₆ (1 mol%), K₂HPO₄ (2.4 equiv.) MeCN (19 mL) and H₂O (1 mL). 24 h, 100 °C, 12 W blue LEDs. Isolated yields. Regioselectivity ratio (*rr*) determined by ¹H NMR. ^a48 h. ^bK₂HPO₄ (3.4 equiv.) was used. ^calkyne (0.25 mmol) was used. ^dalkyne (0.167 mmol) was used. ^ea mixture of regio- and diastereo-isomers, which is difficult to isolate. ^facid (12.0 mmol), alkyne (6.0 mmol), MeCN (120 mL), H₂O (6 mL), 48 h.

applications of these molecules (Fig. 6). Taking indanone **9** as an example, the terminal alkene **91**, 3-phenyl-1*H*-inden-1-one **92**, lactone **93**, and 1-phenyl-2,3-dihydro-1*H*-indene **94** could be obtained via the Wittig reaction, oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), Baeyer–Villiger oxidation, and reduction by Zn/HOAc system, respectively. The methylene group of **9** reacted with an aldehyde to give (*E*)-2-benzylidene-3-phenyl-2,3-dihydro-1*H*-inden-1-one **95** efficiently. Particularly, benzocycloheptenone **96** can be prepared straightforwardly via

the two-carbon ring expansion strategy with inexpensive ethylene developed by Dong's group⁶⁶.

Given that the robust efficiency observed, we next turned our attention to a deeper exploration of the chemo- and regioselectivity of this water-mediated reaction by including different type C–H bonds within various molecular probes (Fig. 7). An initial competition between multiple aryl C–H bonds within a single intermediate illustrates the absolute propensity for generation of indanone **98** (**98** vs. **99**). This observation indicates

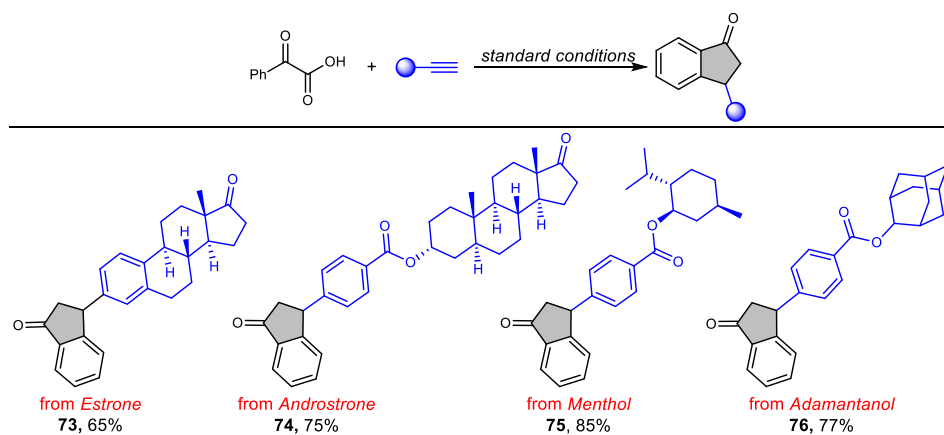


Fig. 4 Late-stage functionalization of complex molecules. Reactions conditions: acid (1.0 mmol), alkyne (0.5 mmol), $\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$ (1 mol%), K_2HPO_4 (2.4 equiv.) MeCN (19 mL) and H_2O (1 mL). 24 h, 100 °C, 12 W blue LEDs. Isolated yields. The diastereometric ratio could not be determined by ^1H NMR analysis.

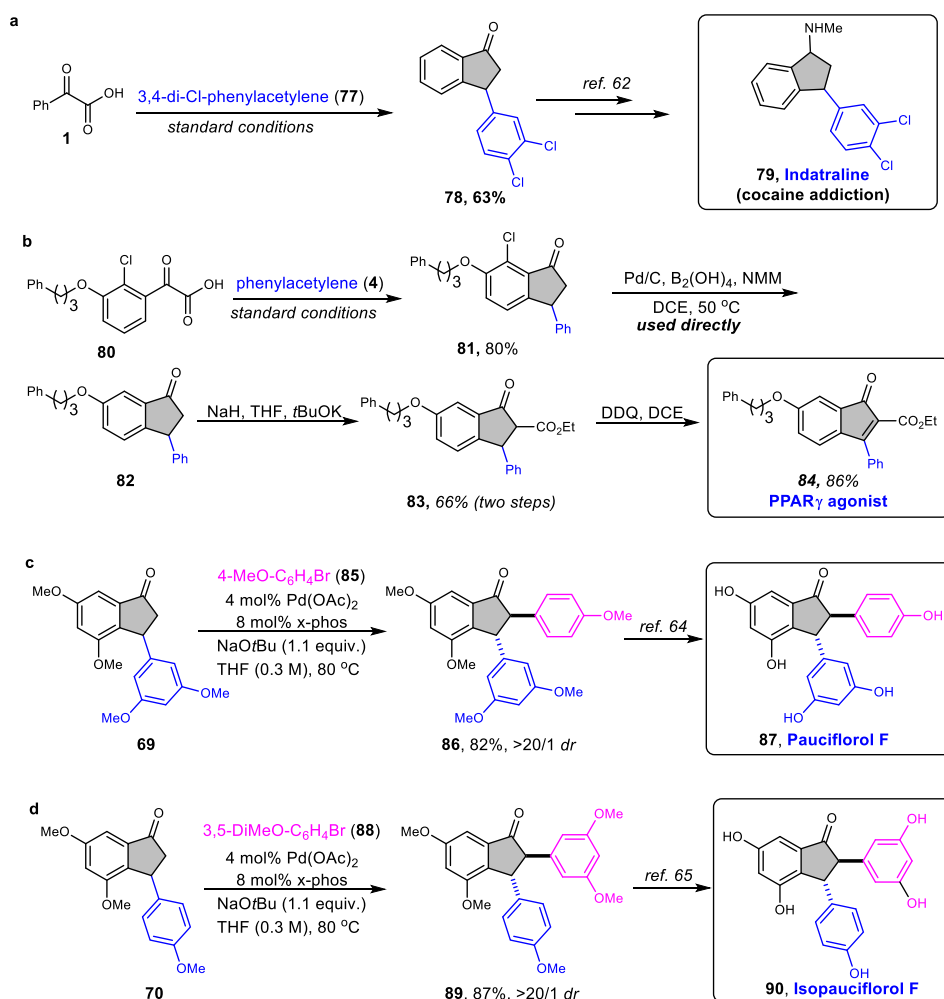


Fig. 5 Synthetic applications of indanones. **a** Key intermediate for indatraline construction could be afforded by the developed protocol. **b** Synthesis of PPAR γ agonist using this strategy. NMM 4-methylmorpholine. **c** Powerful protocol to prepare pauciflorol F. **d** Formal synthesis Isopauciflorol F.

that the carbonyl group plays a key role during the cyclization process to provide a five-membered ring product. We next tested the competition of aryl C–H bonds and weaker Csp³–H bond involved in the intermediate. In these cases, the HAT between

vinyl radical and weaker C–H bonds outcompetes water-mediated pathways affording the furan-derived products with little indanones detected (**101** vs. **102**, **104** vs. **105**, **107** vs. **108**). These phenomena not only showed obvious chemo-selectivity in

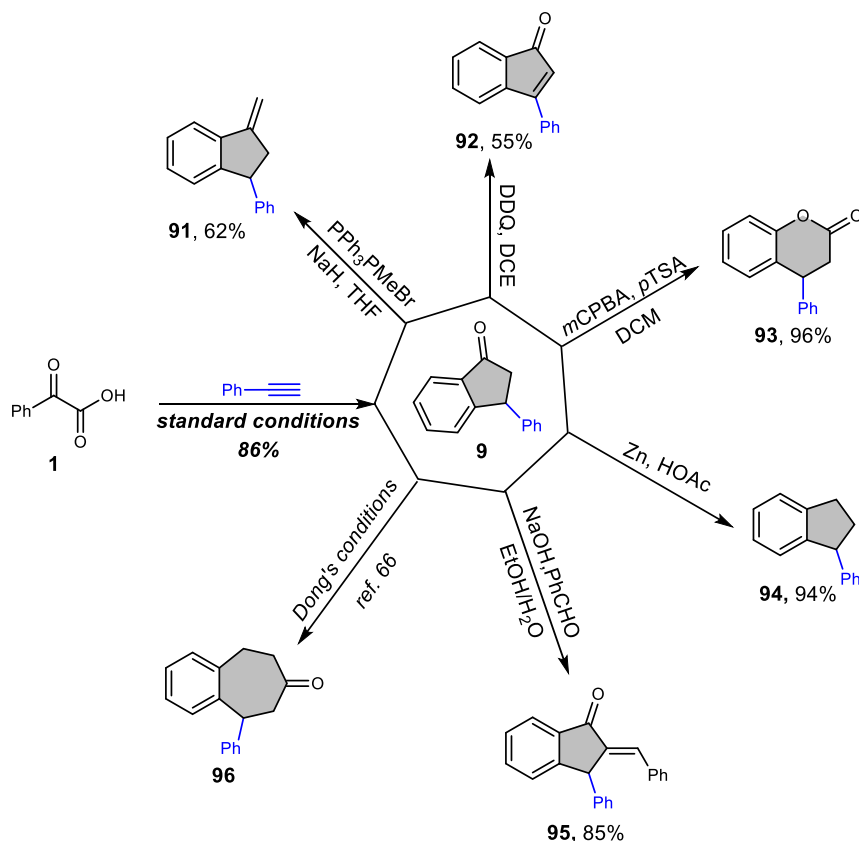


Fig. 6 Further transformations of indanones. The indanone **9** was prepared from **1** under standard conditions. The indanone **9** was efficiently transformed to diverse compounds, such as alkene **91**, indenone **92**, lactone **93**, 1-phenyl-2,3-dihydro-1H-indene **94**, (*E*)-2-benzylidene-3-phenyl-2,3-dihydro-1H-inden-1-one **95**, and benzocycloheptenone **96**, respectively.

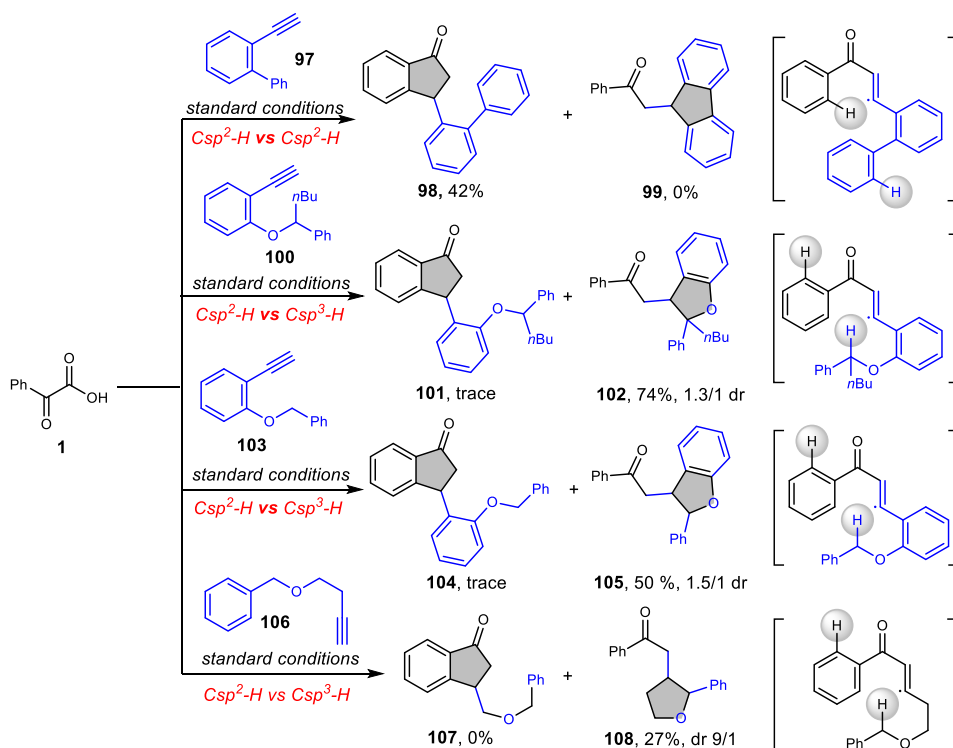


Fig. 7 Mechanistic probes for chemo- and regio-selectivity. Competitions between different C-H bonds. The indanone **98** was formed in the presence of another $\text{Csp}^2\text{-H}$ bond. Only furan-derived products (**102**, **105** and **108**) could be isolated when weaker $\text{Csp}^3\text{-H}$ bonds have existed.

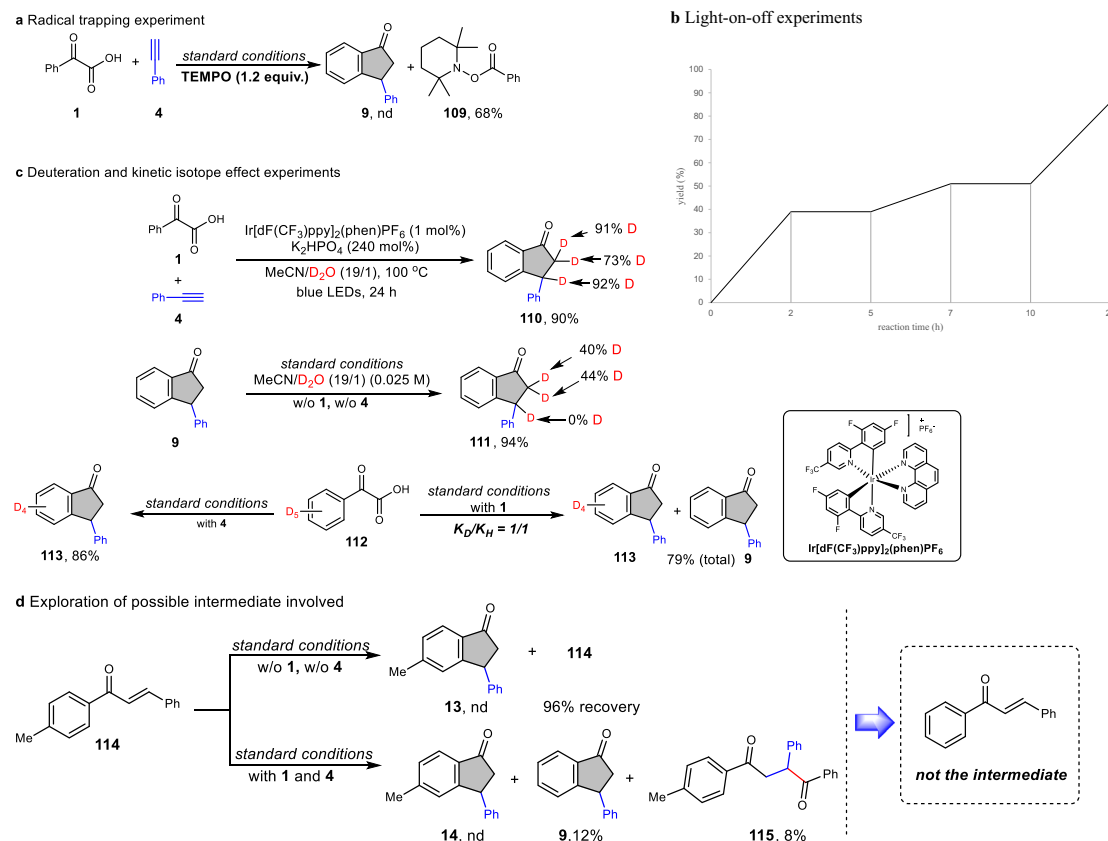


Fig. 8 Mechanistic studies. **a** Radical-trapping experiment with 2,2,6,6-tetramethylpiperidinoxy (TEMPO). **b** Light-on-off the experiment. **c** Deuterated and kinetic isotope experiments. **d** Exploration of possible intermediate involved.

the presence of weaker C–H bonds but also deliver strong evidence for the existence of vinyl radical. Moreover, the deuterium substitution experiment with D_2O using substrate **100** was performed and found that no deuterated benzylic product was formed (see Supplementary Fig. 1 for details). The result indicated that the corresponding product was formed through an intramolecular 1,5-HAT followed by a Giese addition, which is not a water-mediated pathway.

To better understand the detailed mechanism of the reaction, a series of mechanistic studies were performed (Fig. 8). In the presence of radical trap TEMPO, the reaction was completely shut down (Fig. 8a), indicating that a radical intermediate might be involved in this transformation. More importantly, acyl-trapped product, 2,2,6,6-tetramethylpiperidin-1-yl benzoate **109** was isolated in high yield, further supporting the reaction proceeds through a radical decarboxylation pathway and the intermediacy of an acyl radical. The light-on-off experiment demonstrates the radical chain mechanism is less likely involved (Fig. 8b). To verify if H_2O was involved in the reaction as proposed, D_2O was used and subjected to the optimal reaction conditions, deuterated product **110** was observed in 90% yield when D_2O was utilized in place of H_2O , demonstrating the benzylic site of hydrogen is originated from water (Fig. 8c, top). To further test whether deuterated product **110** was generated from the indanone **9** under standard conditions through H/D exchange with D_2O , indanone **9** was subjected to the reaction conditions with D_2O instead of H_2O (Fig. 8c, middle). Interestingly, a deuterated indanone **111** was formed, in which only the CH_2 of indanone was deuterated through H/D exchange with D_2O and no deuterated benzylic product was formed. This experiment suggested that the benzylic C–H cannot be deuterated through H/D exchange with D_2O under standard conditions. To verify whether the 1,5-

HAT is involved in the reaction, deuterated phenylglyoxylic acid **112** was used as substrate under standard conditions (Fig. 8c, bottom, left). The absolute indanone **113** without deuterium transfer was obtained in 86% yield, demonstrating that the reaction did not proceed via 1,5-HAT pathway. In addition, it also indicated that no obvious direct hydrogen transfer occurred from the aryl position to the corresponding methylene and benzylic site of indanone, which is not in line with the 1,2- and 1,3-HAT. Taken together, the hydrogen atom of benzylic C–H of indanone should come from water during the catalytic reaction process, neither from the aryl C–H via 1,5-HAT nor from water through H/D exchange after reaction completion. Kinetic isotope experiments (KIE) were also performed to have more insight into the reaction mechanism (Fig. 8c, bottom, right). Since no obvious KIE effect ($K_D/K_H = 1/1$) was detected when the equivalent of **1** and **112** were subjected to the reaction conditions with alkyne **4**, according to the intermolecular competition experiment, aryl C–H bond cleavage was not likely the rate-determining step. Additionally, when ketone **114** was performed under standard conditions, no cyclized product **13** was detected but with a recovery of **114** in 96% (Fig. 8d, top). Furthermore, when chalcone **114** was added as an additive to the model reaction, only the predictable indanone **9** and Giese-type reaction product **115** could be monitored (Fig. 8d, bottom). These control experiments strongly indicated that the chalcone **114** is less likely the intermediate involved in the reaction.

DFT calculation was subsequently employed to provide further insight into the mechanism of this decarboxylative annulation reaction (Fig. 9a). According to the computational calculations, an intermolecular radical addition with phenylacetylene **4** takes place via transition state **TS1** with a free energy barrier of 23.7 kcal/mol to afford the vinyl radical **5**. Then an intramolecular radical addition

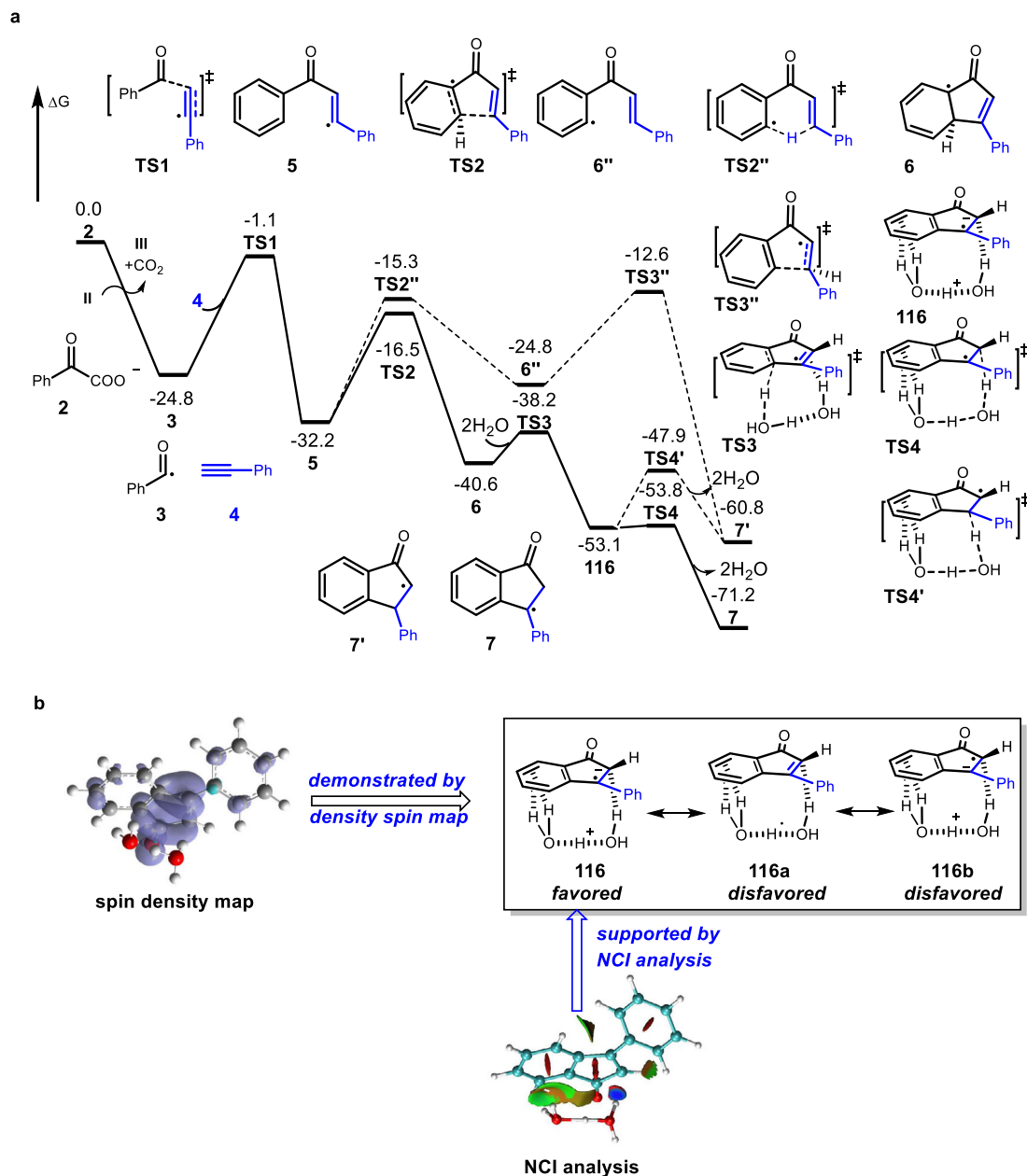


Fig. 9 The free energy barrier for the reaction and the spin density and noncovalent interaction (NCI) analysis for the intermediate **116**. **a** Computational studies. **b** The spin density map and NCI analysis for the intermediate **116**.

would occur via transition state **TS2** with a free energy barrier of 15.7 kcal/mol to achieve annulation and form a dearomatized intermediate **6**. Because of the similar BDE values of C–H bonds between alkenes and arenes, we considered an alternative intramolecular 1,5-hydrogen shift theoretically via transition state **TS2''**. However, the relative free energy of generated phenyl radical **6''** is 7.4 kcal/mol higher than that of vinyl radical **5**. Moreover, the relative free energy for the corresponding annulation transition state **TS3''** is also 3.9 kcal/mol higher than that of **TS2**. This analysis revealed that the generation of intermediate **6** is a favorable pathway. These calculations were highly consistent with our experimental observations (Fig. 8c). Next, we focused on understanding the exact role of water in the formation of intermediate **7** or **7'**. When dearomatized intermediate **6** is formed, from calculations, a water-assisted stepwise 1,3-hydrogen transfer would provide a more stable benzylic radical **7** with rearomatization. In this process, two water molecules were used to achieve dehydrogenation via transition state

TS3 to afford a complex radical intermediate **116** with a free energy barrier of only 2.4 kcal/mol (see Supplementary Fig. 9 for other water molecules assisted pathway). Two other possible resonance structures of intermediate **116** could be drawn as electron-neutral indenone with hydrated hydrogen radical **116a** and zwitterionic in indenolate radical with protonated water **116b**. The spin density map of intermediate **116** clearly revealed that spin density is majorly located at indenone moiety. Meanwhile, the electrostatic potential map also exhibits a charge-separated character (Fig. 9b). Therefore, zwitterionic resonance structure **116** has a more appreciable contribution for this intermediate. Interestingly, noncovalent interaction (NCI) analysis of intermediate **116** also revealed a strong hydroxyl– π interaction between indenolate radical and hydrated proton, which explained the stability of this intermediate. When intermediate **116** is formed, a rapid protonation takes place via transition state **TS4** resulting in the formation of benzylic radical **7** with the release of two water molecules (see Supplementary Data 1

for the coordination of all the structures involved in the computational calculations). Therefore, as we designed, water acts as a hydrogen radical-shuttle catalyst, promoting the favorable 1,3-hydrogen transfer with the formation of intermediate 7.

In summary, we have developed a decarboxylative annulation for indanones synthesis via photoredox/HAT catalysis with water as hydrogen radical-shuttle (HRS). This protocol provides a powerful platform to construct indanones with broad substrate scope, excellent functional group tolerance, internal hydrogen radical transfer, atom- and step-economy, using simple and available 2-oxo-2-phenylacetic acids and readily available alkynes. Moreover, the exact role of water in this developed strategy was demonstrated by mechanistic experiments and DFT calculations, as we designed, facilitating the hydrogen transfer and acting as the hydrogen source. Namely, acting as a HRS catalyst was critical to the success of this process. Additionally, the key intermediate **116** was further demonstrated by spin density map and NCI analysis. Most importantly, to the best of our knowledge, this system provides an aromatization model, representing a breakthrough in hydrogen radical transfer assisted by HRS. This hydrogen transfer is mechanistically distinctive from that of typical PS-promoted, providing a complementary process in hydrogen transfer and a feasible solution in achieving 1,2-, or 1,3-HAT. We expect this strategy could be widely adopted and further promote the development of direct functionalization of aryl Csp^2 -H via HRS-assisted hydrogen transfer.

Methods

Materials. Unless otherwise noted, all the materials were obtained commercially and used without further purification. All the solvents were treated according to general methods. Flash column chromatography was performed over silica gel (300–400 mesh). See Supplementary Methods for experimental details.

General procedures for the indanones synthesis. To an oven-dried 50 mL flask, $Ir[dF(CF_3)ppy]_2(phen)PF_6$ (0.005 mmol), 2-aryl-2-oxocarboxylic acid (1.0 mmol) and K_2HPO_4 (1.2 mmol) were added sequentially under N_2 . The flask was evacuated and back-filled with N_2 for three times, then alkyne (0.5 mmol), H_2O (1 mL), and MeCN (19 mL) was added. The reaction mixture was irradiated by 12 W blue LEDs at a distance of 5 cm for 24 h at 100 °C. The reaction mixture was cooled to rt and filtered through a short pad of silica using ethyl acetate. The filtrate was concentrated in vacuo before it was purified by flash chromatography on silica gel to afford the desired indanone product.

Computational method. All the calculations in this study were performed using the Gaussian 16 program package.⁶⁷ The All the geometries were optimized at the M06-2X⁶⁸/6–31 G(d,p) and SDD for Ir level, and the solvent effect was utilized the polarizable continuum model using integral equation formalism model (IEFPCM) in hexane solvent.⁶⁹ All the optimized stationary points had been identified as minima (zero imaginary frequencies) and transition states (one imaginary frequency), via the vibrational analysis. The solution-translational entropy correction has been calculated with the THERMO program.⁷⁰

Data availability

The authors declare that the data relating to the characterization of materials and products, general methods, optimization studies, experimental procedures, mechanistic studies, HRMS data and NMR spectra, computational studies are available within the article and its Supplementary Information as well as supplementary data.

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Author contributions

B.Y. and S.Z. designed the experiments. B.Y. performed experiments. S.-J.L. and Y.L. performed DFT calculations and wrote the paper's DFT calculations. S.Z. and Y.W. co-directed the synthetic applications of indenones. B.Y. wrote the paper and S.Z. revised-reviewed & edited the paper. All authors discussed the results and commented on the manuscript. S.Z. directed the whole project.

Competing interests

The authors declare no competing interests.

Additional information

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Direct synthesis of dialkyl ketones from deoxygenative cross-coupling of carboxylic acids and alcohols†

Bo Yang *^{ab} and Ri-Yuan Tang *^{ab}

Carboxylic acids and alcohols are widely commercially available, structurally diverse, benchtop stable, and ubiquitous in both natural products and pharmaceutical agents, making them ideal coupling partners for organic synthesis. Though various transformations have been developed by enabling the activation and subsequent cross-coupling of carboxylic acids and alcohols in separate contexts, the direct coupling of these two structural motifs to build value-added molecules is rare. Herein, we developed a direct deoxygenative cross-coupling between carboxylic acids and alcohols for dialkyl ketone synthesis *via* photoredox/nickel dual catalysis. This protocol provides a powerful platform to construct a wide range of structurally diverse ketone scaffolds with broad substrate scope, good functional group tolerance, step-economy and mild reaction conditions, using simple and readily available substrates. Moreover, the large-scale synthesis and late-stage functionalization of biological molecules also demonstrate the potential practicality.

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Due to the prevalence of ketones in natural products and bioactive drugs¹ and their central role as versatile reactants in synthetic chemistry,² the development of powerful methods for ketone synthesis is highly desirable. In this context, a vast number of methods have been developed to construct ketones. Typically, ketone synthesis most often relies upon the addition of an organometallic reagent to an aldehyde followed by oxidation³ or more recently, the use of carboxylic acid derivatives to couple with various nucleophiles (Fig. 1a).⁴ While significant contributions have been made to this field, these methods typically necessitate a prefunctionalization step and often require nonabundant starting materials, such as air- and moisture-sensitive alkyl organometallics,^{4e,k-l} and organoboron and organosilicon reagents,^{4c-e} which are not step-economical and might lead to issues with functional group tolerance and waste generation, thereby limiting the reaction scope and practicality. To address this problem, we sought to develop a robust platform to deliver ketones utilizing easily accessible and commercially available starting materials under mild conditions.

Carboxylic acids and alcohols are widely commercially available, structurally diverse, benchtop stable, relatively

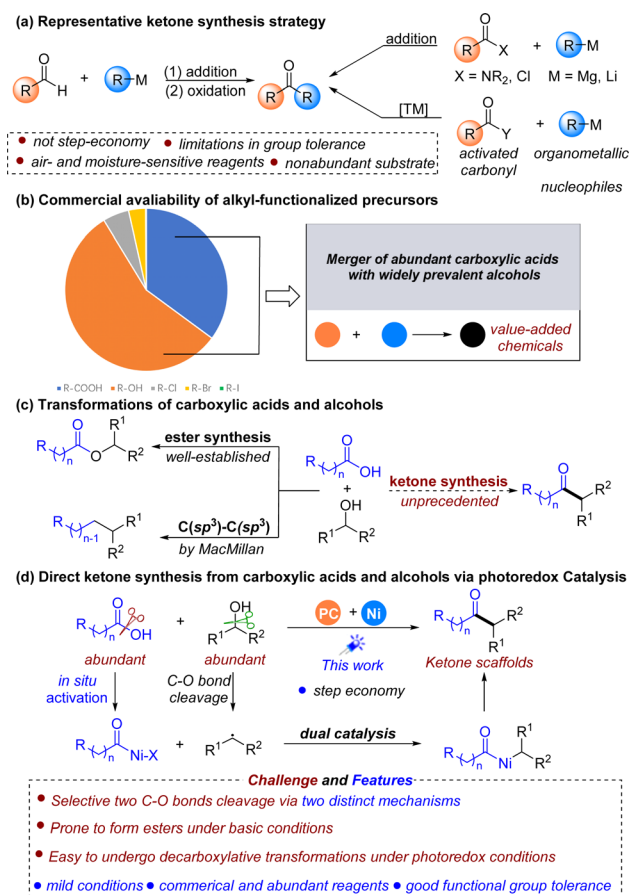


Fig. 1 Background of ketone synthesis and cross-coupling of carboxylic acids and alcohols.

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nontoxic, and ubiquitous in both natural products and pharmaceutical agents,⁵ making them ideal coupling partners for organic synthesis (Fig. 1b). In recent years, a variety of transformations have been developed by enabling the activation and subsequent cross-coupling of carboxylic acids and alcohols *via* metallaphotoredox catalysis in separate contexts.⁶ The direct coupling of these two prevalent structural motifs to build value-added molecules is significantly rare but highly of interest. Conventionally, alcohols and carboxylic acids are most commonly coupled to form esters,⁷ and fragment cross-coupling of these two structural motifs has been explored to a lesser extent. Recently, the efficient direct coupling of carboxylic acids and alcohols to forge new C(sp³)-C(sp³) bonds has been developed *via* an N-heterocyclic carbene (NHC)-promoted deoxygenation process by the MacMillan group (Fig. 1c, left).⁸ Despite this great achievement, developing new types of cross-coupling reactions between these two molecules has remained an appealing yet elusive goal. Considering the importance of ketone scaffolds, we wondered if diverse ketones could be accessed from the direct coupling of abundant carboxylic acids and alcohols, where acids serve as acyl electrophiles, and alcohols serve as nucleophiles (Fig. 1c, right). On this subject, Hong developed a photoinduced method for synthesizing ketones from alcohols and carboxylic acid derivatives through NHC catalysis under mild reaction conditions.^{6g} This approach worked well for benzoic acid, but was not effective for the alkanolic acid substrates. As a consequence, developing an efficient and new catalytic methodology to convert carboxylic acids and alcohols into dialkyl ketone scaffolds is still highly of interest and would complement Hong's strategy.

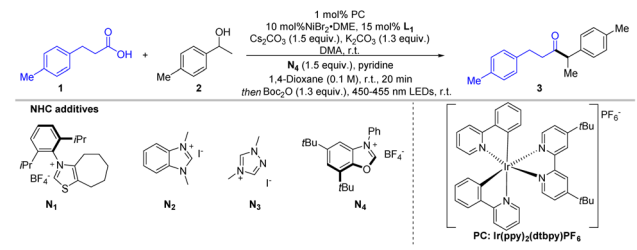
However, direct coupling of these two structural motifs forming ketones in a desired manner is not as easy as might be expected due to the potential competing cleavage of two C-O bonds in these two molecules. The main challenge for realizing this transformation was how to selectively achieve C-O bond cleavage in both alcohols and carboxylic acids *via* two distinct mechanisms. In recent years, the combination of photoredox and nickel catalysis has emerged as a powerful tool in chemical bond construction,⁹ which might provide an alternative protocol for the ketone preparations from alcohols^{10,11} and acids. In such a reaction, a transition-metal catalytic unit could engage sequentially with the acyl electrophiles formed *in situ* from carboxylic acids¹² and radicals generated from alcohols through oxidative addition¹³ and radical capture.^{12a,14} Then the resulting diorganonickel adduct undergoes reductive elimination to afford the desired ketone scaffolds (Fig. 1d). Nevertheless, to achieve this goal, other potential competing reactions, such as the esterification reaction^{6f} and decarboxylative transformation,^{15,6e,h,i} which are commonly encountered under basic and photoredox conditions, are also a big problem and need to be avoided.

In this work, we developed a photoredox-catalyzed synthetic protocol for diverse dialkyl ketone synthesis from naturally abundant carboxylic acids and alcohols under mild conditions with good functional group compatibility, and broad substrate scope. This protocol features no protection and deprotection steps. Given the structural diversity of carboxylic acids and

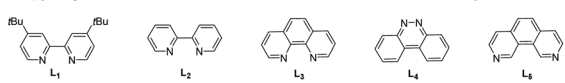
alcohols, the success of this protocol could potentially enhance the synthesis of complex ketones. More significantly, ketones can be directly constructed from two abundant starting materials, thus expanding the existing ketone synthetic routes.

To start our investigation, the synthetic method for ketones was explored with the commercially available carboxylic acid **1** and alcohol **2** as the model substrate (Table 1). Based on previously reported elegant carboxylic acid activations in ketone synthesis,^{6h,j,12a,14} Boc₂O was chosen as the activating reagent to generate mixed anhydride *in situ* from carboxylic acids. After extensive reaction condition screening (see the ESI† for details), we were pleased to find that the corresponding ketone **3** was obtained in 73% isolated yield using **N4** as the alcohol-activating agent and Cs₂CO₃/K₂CO₃ and pyridine as bases in the presence of a catalytic amount of NiBr₂·DME and **L1** under visible light irradiation in DMA/1,4-dioxane using Ir(ppy)₂-(dtbbpy)PF₆ as the photocatalyst (entry 1). The thiazole-based NHC reagent **N1** and other simple triazole-based NHC molecules **N2** and **N3** are ineffective in this transformation (entry 2). These initial optimization studies revealed the importance of NHC types for the reaction efficiency. A slightly lower yield was obtained when *t*BuOMe was used instead of 1,4-dioxane (entry 3). Other solvents, such as benzotrifluoride, tetrahydrofuran and acetonitrile were also tested and the results indicated that

Table 1 Optimization of reaction conditions^a



Entry	Variation from optimized conditions	Yield ^b (%)
1	None	75 (73)
2	N1 , N2 , and N3 instead of N4	0, trace, 0
3	BuOMe instead of 1,4-dioxane	60
4	PhCF, THF, and MeCN instead of 1,4-dioxane	54, 13, <10
5	L2 , L3 , L4 , and L5 instead of L1	37, 32, 30, trace
6	5 mol% NiBr ₂ ·DME, 7.5 mol% L1	78 (75)
7	No light irradiation	0
8	No NHC	0
9	No PC	0



^a Reaction conditions: **1** (0.3 mmol), **2** (0.42 mmol), 1 mol% Ir(ppy)₂(dtbbpy)PF₆, 10 mol% NiBr₂·DME, 15 mol% **L1**, Cs₂CO₃ (0.45 mmol), K₂CO₃ (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc₂O (1.3 equiv.), 450–455 nm LEDs.

^b Yields of **3** were determined by ¹H NMR spectroscopy with mesitylene as an internal standard and the isolated yield is shown in parentheses. r.t., room temperature; NHC, N-heterocyclic carbene; DME, 1,2-dimethoxyethane; DMA, *N,N*-dimethylacetamide.



1,4-dioxane was more suitable for this transformation (entry 4). Screening of a range of ligands revealed that acylation product **3** could also be generated, albeit in diminished yields (entry 5). A slight increase in the yield was observed on reducing the amount of $\text{NiBr}_2 \cdot \text{DME}$ and **L1** (entry 6). Light irradiation was essential for this transformation as it did not progress under dark conditions (entry 7). Further control experiments showed that NHC and the photocatalyst were indispensable in this transformation (entries 8–9). It was worth noting that the side products due to decarboxylation and esterification could be detected.

With the optimized reaction conditions in hand, we then investigated the scope of carboxylic acids and alcohols (Fig. 2). We first probed the ability of various aliphatic acids for cross-coupling in our system (3–22). Substituted phenyl propionic acid and butyric acid derivatives yielded desired products in moderate to good yields (3–10). A range of aliphatic acids, including linear and cyclic acids, were amenable substrates, providing the cross-coupling products in good to excellent yields (11–18). Notably, carboxylic acids with additional functionalities were also compatible with this protocol. For example, various functional groups, such as alkyl chloride, ester, protected amine and ketone remain intact to furnish the

corresponding cross-coupling products, potentially allowing for the subsequent orthogonal functionalization (15–19). In particular, carboxylic acids with synthetic handles, such as halide (**10** and **15**), were readily incorporated into the accessible ketone scaffolds, which highlights the potential applications for the incorporation of these scaffolds into more complex targets. Products derived from alkenyl acids were also tolerated, as demonstrated by β,β -dimethylacrylic acid (**20**) and lineoic acid (**21**). These results show the great potential for structural modification and resource utilization of naturally existing carboxylic acids. Heterocycle-containing carboxylic acid reacted smoothly in this system, affording the deoxygenated cross-coupling product in moderate yield (**22**). Of particular note is that substituted phenyl acetic acid and hindered carboxylic acids (**23**), such as *N*-Boc proline (**24**) and 2-phenyl propionic acid (**25**) were not suitable for this transformation, yielding no product. Additionally, experiments with various benzoic acid derivatives were also performed under the standard conditions. Unfortunately, these substrates were not compatible with our system (**26–27**). This phenomenon could be attributed to the diminished reactivity in carboxylic acid activation.

Having established that this transformation tolerates various carboxylic acids, we turned our attention towards evaluating the scope of alcohol components. Consistent with our expectation, we were pleased to find that a wide variety of primary alcohols were successfully applied in this protocol, furnishing the desired ketones in moderate yields (28–32). The instability of the corresponding alkyl radicals originating from alcohols could be responsible for the relatively lower yield (29–32). Of particular note is that the developed protocol was also tolerant of the alcohol containing protected amine, as demonstrated by **31**, which was isolated in 40% yield. Notably, the alkene-retained product (**32**) was obtained in 39% yield, while intramolecular radical cyclization was not observed. This result suggests the faster capture of the alkyl radical than 5-*endo*-trig cyclizations under the specific reaction conditions. Secondary alcohols, especially cyclic alcohols, ranging from four- to seven-membered rings, were found to be viable coupling partners, successfully delivering the corresponding products in 40–61% yields (33–38). It is noteworthy that sterically encumbered polycyclic alcohols, such as 2-adamantanol, were employed without an appreciable decrease in the reaction efficiency (37). A relatively increased yield was obtained when benzyl alcohols were used, which is in line with the stability of the corresponding radical intermediates from alcohols (38–41). With these positive results in hand, we finally tested the feasibility of tertiary alcohols, such as 1-methylcyclohexanol and *tert*-butanol, and the experimental results indicated that no corresponding cross-coupling product could be observed (42–43).

Given the exceptionally mild and simple conditions, we sought to demonstrate the utility of this operationally convenient method in the late-stage functionalization of complex molecules. As shown in Fig. 3, the oxaprozin analogue **44** could be generated efficiently with our strategy in 55% yield. Lithocholic acid analogues could also undergo smoothly, providing the deoxygenative ketone in 60% and 62% yield, respectively (45 and 46). With stearic acid as an acyl donor, the

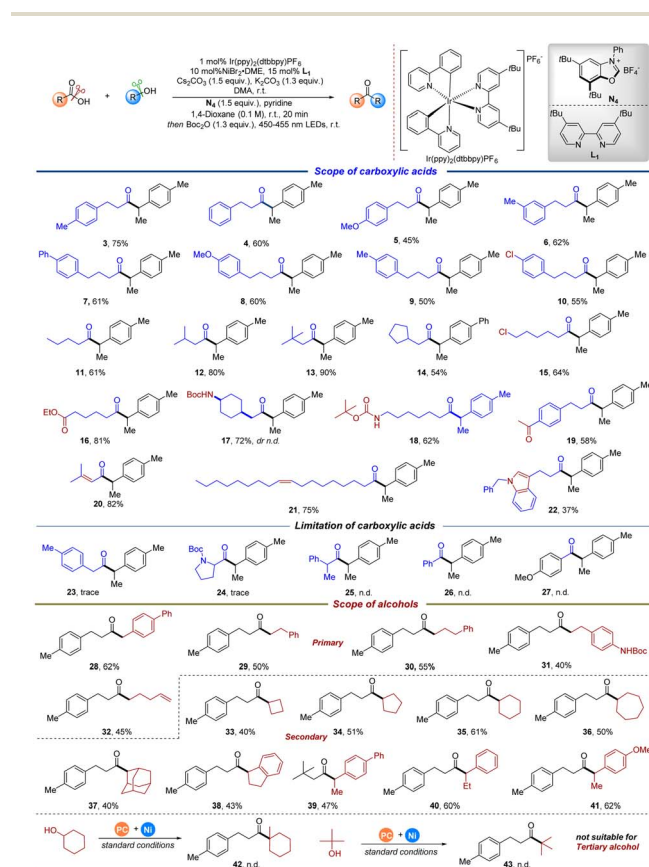


Fig. 2 Substrate scope for ketone synthesis. Standard conditions: carboxylic acid (0.3 mmol), alcohol (0.42 mmol), 1 mol% $\text{Ir}(\text{ppy})_2(\text{-dtbbpy})\text{PF}_6$, 10 mol% $\text{NiBr}_2 \cdot \text{DME}$, 15 mol% **L1**, Cs_2CO_3 (0.45 mmol), K_2CO_3 (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc_2O (1.3 equiv.), 450–455 nm LEDs. Isolated yield.



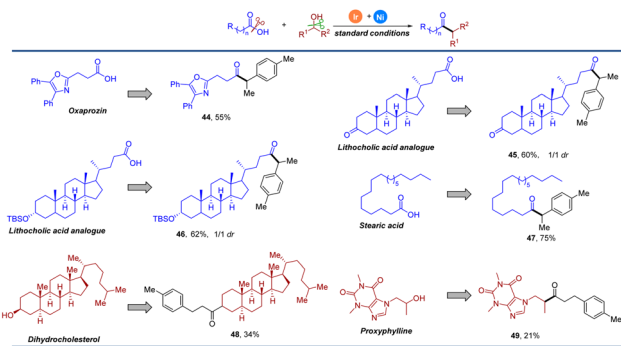


Fig. 3 Late-stage functionalization. Standard conditions: carboxylic acid (0.3 mmol), alcohol (0.42 mmol), 1 mol% $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$, 10 mol% $\text{NiBr}_2 \cdot \text{DME}$, 15 mol% L_1 , Cs_2CO_3 (0.45 mmol), K_2CO_3 (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc_2O (1.3 equiv.), 450–455 nm LEDs. Isolated yield.

transformation proceeded efficiently, yielding **47** in 75% yield. A naturally occurring steroid was also successfully employed and afforded the corresponding product **48** in moderate yield. Bronchodilator proxiphylline showed good reactivity to deliver the product **49** in 21% yield. These results show great potential for the structural modification of an array of complex biological molecules, especially in medicinal chemistry.

To further showcase the synthetic utility of this developed strategy, a large-scale experiment was conducted, providing the desired ketone **3** in 71% yield (Fig. 4). There was almost no change in the chemical yield, suggesting that large-scale chemical production might be possible.

To gain further insight into the reaction mechanism, a series of mechanistic studies were performed (Fig. 5). In the presence of radical trap TEMPO, the reaction was completely shut down (Fig. 5a), indicating that a radical intermediate might be involved in this transformation. More importantly, a benzyl-trapped product, 2,2,6,6-tetramethylpiperidin-1-yl benzoate **50** was observed *via* high resolution mass spectrometry, further supporting that the reaction proceeds through a radical deoxygenative pathway and the intermediacy of a benzylic radical. Furthermore, the generation of a benzylic radical from **2** in the reaction also could be demonstrated by the observation of **51** when phenyl vinyl sulfone was added to the system. Additionally, to further elucidate the possible reaction pathway, a radical clock experiment was performed with cyclopropanemethanol **52** and the observation of ring-opening product **53** suggested the involvement of a radical intermediate (Fig. 5b). In our hypothesis, carboxylic acid is activated by Boc_2O , leading to the corresponding acyl-Ni oxidative insertion complex. The control experiments are consistent with this hypothesis. First, when

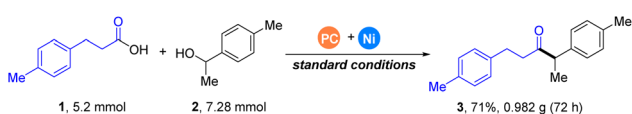


Fig. 4 Large-scale synthesis.

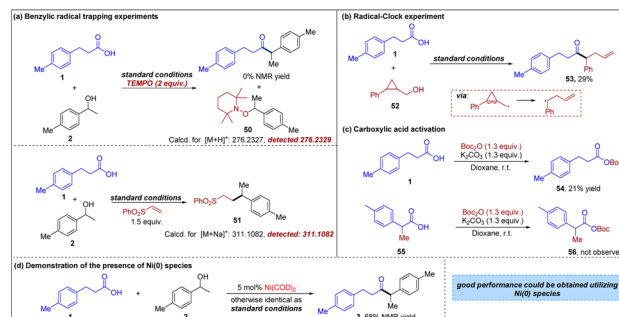


Fig. 5 Mechanistic studies.

primary carboxylic acid **1** is treated with Boc_2O and K_2CO_3 , moderate conversion to the expected mixed anhydride is observed within 3 h (Fig. 5c). In the parallel experiment using secondary carboxylic acid **55**, there is no observable formation of the mixed anhydride **56** at the same time point, resulting in the formation of the acyl-Ni complex being difficult. These results are in line with the limitations of carboxylic acids shown in Fig. 2. It is noteworthy that the desired ketone **3** could be detected in 68% NMR yield when $\text{Ni}(\text{COD})_2$ was used in place of $\text{NiBr}_2 \cdot \text{DME}$ (Fig. 5d), indicating the presence of $\text{Ni}(0)$ species.

Based on the previously reported literature^{6d,f,16} and the aforementioned mechanistic studies, a plausible mechanism for this transformation is proposed in Fig. 6. The proposed mechanism starts with the condensation of alcohol and NHC (**N4**), providing activated alcohol **57**. Upon irradiation with visible light, the photocatalyst $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ **I** is known to access the highly oxidizing excited state species **II** ($^*\text{Ir}^{\text{III}}$ ($E_{1/1}^{\text{red}} \text{ } ^*\text{Ir}^{\text{III}}/\text{Ir}^{\text{II}} = +0.66 \text{ V vs. SCE}$),¹⁷ which could be reductively quenched by the activated alcohol **57**, affording aminium radical cation **58**. Then a deprotonation process occurred at the α -position of **58**, yielding radical intermediate **59**. Subsequent β -scission occurred, thus generating the key alkyl intermediate **60**. The nickel catalytic cycle is initiated by the oxidative addition of the $\text{Ni}(0)$ catalyst **62** to an *in situ*-activated carboxylic acid **61** formed by Boc_2O under basic conditions, to afford $\text{Ni}(\text{II})$ species **64**. Subsequently, efficient trapping of the alkyl radical

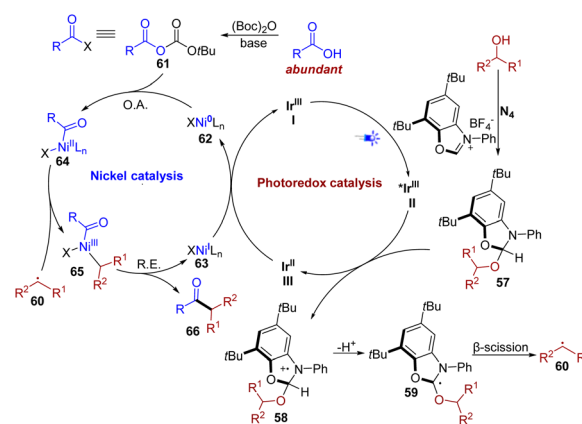


Fig. 6 A plausible mechanism.

60 provides Ni(III) complex **65**, which undergoes reductive elimination to yield the desired ketone **66** and Ni(I) complex **63**. Finally, the single electron transfer between Ni(I) species **63** and reduced photocatalyst **III** (Ir^{II}) regenerates the ground-state photocatalyst **I** (Ir^{III}) and the Ni(0) catalyst, completing both catalytic cycles.

Conclusions

In summary, we have developed a direct deoxygenative cross-coupling between carboxylic acids and alcohols for ketone synthesis *via* photoredox/nickel dual catalysis under mild conditions. This protocol provides a powerful platform to construct a wide range of structurally diverse ketone scaffolds with broad substrate scope, good functional group tolerance, step-economy and mild reaction conditions, using simple and readily available carboxylic acids and widely abundant alcohols as starting materials. Given the structural diversity of carboxylic acids and alcohols, the success of this metal-photoredox-catalyzed deoxygenative cross-coupling protocol could potentially enhance the synthesis of complex ketones. In addition, this developed method will promote the resource utilization of naturally abundant acids and alcohols and enhance the preparation of ketone scaffolds. The exact roles of carboxylic acids and alcohols were demonstrated by mechanistic studies, as we hypothesized, that the carboxylic acids provide the acyl group and the alcohols afford the alkyl group. Asymmetric transformations of carboxylic acids and alcohols into ketones are underway in our laboratory and will be reported in due course.

Data availability

The ESI† is available and includes experimental procedures for all reactions and characterization data for all products, including ¹H and ¹³C spectra and HRMS data.

Author contributions

Conceptualization and funding acquisition were done or provided by B. Y.; resources and supervision were done by B. Y.; project administration, data curation, investigation and formal analysis were done by B. Y. and R.-Y. T.; writing was done by B. Y. and revised by B. Y. and R.-Y. T.

Conflicts of interest

There are no conflicts to declare.

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Bifunctional two-carbon reagent made from acetylene *via* 1,2-difunctionalization and its applications

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There are very limited approaches to directly gluing two molecules for the production of internal alkenes using the vastly abundant acetylene *via* 1,2-difunctionalization. Conversion of gaseous acetylene to internal alkenes *via* 1,2-difunctionalization in a desired manner is not as easy as it might be expected due to the potential competition reactions between acetylene and alkene produced and the difficulty in handling this harmful reagent and controlling the regio- and stereoselectivity. In this work, we designed an efficient catalytic system for the incorporation of acetylene gas into tremendous (*E*)- β -bromo vinylsulfones, which are bench-stable, easy to operate, and can function as bifunctional acetylene and show a rich reactivity profile in Sonogashira coupling, Heck coupling, substituted reaction, and various desulfonylation transformations, providing numerous internal alkenes.

acetylene, 1, 2-difunctionalization, photocatalysis, vinylsulfone

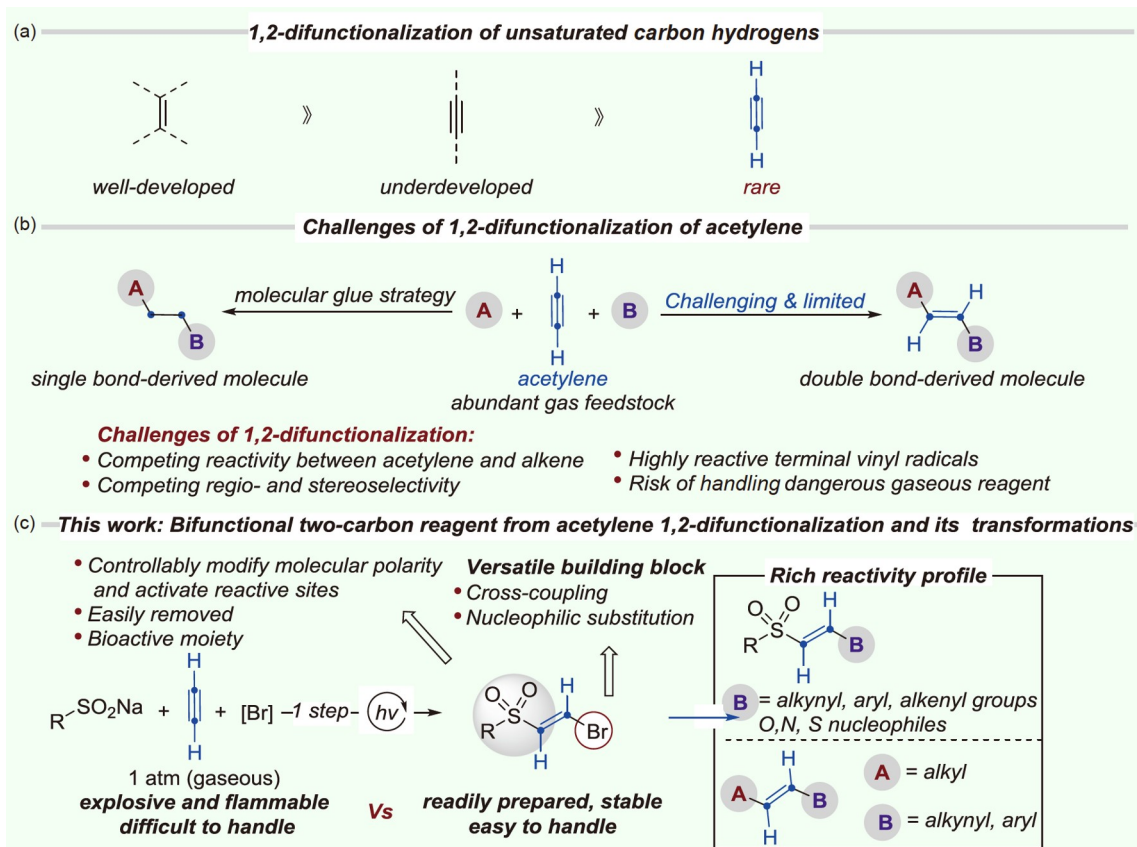
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1 Introduction

Due to the rich chemistry of alkenes, the presence of an alkenyl substituent allows a great variety of possibilities for diversification and elaboration *via* functionalization. Therefore, conventional approaches to alkenes, such as the well-known Wittig reactions [1], alkene metathesis [2], alkyne functionalization [3], Heck-type reactions [4], and many others [5], have been well developed. Among these strategies, direct functionalization, particularly 1,2-difunctionalization of alkynes, is an attractive approach for rapidly constructing the desired alkenes in a convenient and economical pathway. However, alkyne 1,2-difunctionalization is not well developed compared with alkene 1,2-difunctiona-

lization. This scenario can probably be ascribed to regio- and stereoselectivity (Scheme 1a) [6]. As the simplest alkyne, acetylene is a vastly abundant and cheap commodity feedstock [7]; however, the catalytic transformations of this harmful two-carbon unit in organic synthesis are quite limited [8]. This is, to some extent, due to the difficulty of handling the explosive and flammable gaseous reagent, which has historically frustrated their utilization in synthesis. Another reason is that the broad knowledge available for substituted alkynes is often not directly transferable to acetylene due to its intrinsic stronger strength of the π -bonds and higher activation energies for reactions [8d,8k]. Furthermore, the instability of its possible intermediates, terminal vinyl radical [9,10], and especially the cation [11], has traditionally restricted its conversion. At present, acetylene has been employed as a feedstock for the preparation of bulk

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Scheme 1 Strategies for incorporating acetylene into fine chemicals (color online).

chemicals, such as vinyl chloride monomer, vinyl acetate, acetaldehyde, acrylonitrile, and other products [8a]. Also, it can take part in other transformations, such as nucleophilic addition [8c,12], [2+n] cyclization [13,14], cross-coupling [15], and di-/tri-/polymerization reaction [8a,8g,8h,16]. To effectively introduce acetylene in synthesis, competing reactions, such as the formation of more reactive substituted alkynes or alkenes from acetylene, need to be prevented. Despite these developments, effective catalytic protocols to incorporate acetylene into fine chemicals are still limited.

In fact, due to the existence of the two addressable π -bonds, acetylene is still one of the simplest, readily functionalized, and ideal two-carbon synthons. Notably, various functionalized vinyl molecules are prepared *via* mono-functionalization using acetylene [8a,8i,13,17]. Nevertheless, the difunctionalization of acetylene is relatively rare [8a–8c,18]. On this subject, we have recently developed three radical difunctionalization protocols of acetylene through a molecular glue strategy [8c,18b,18c]. However, the focus of these protocols is on constructing single bond-derived molecules *via* cascade transformation (Scheme 1b, left). Considering our immense interest in acetylene transformation [8b,8c,16c,17d,18,19], we wondered if 1,2-difunctionalization of acetylene involving the radical process

could allow the rapid synthesis of double bond-derived products, such as internal alkenes (Scheme 1b, right). With this in mind, recently, we have designed a 1,2-difunctionalization method that introduces acetylene directly into readily available bifunctional reagents (two components) using a photocatalyzed process [18d]. Although powerful, this strategy has drawbacks, such as requiring pre-functionalization of bifunctional reagents and having a limited substrate scope (O/S/Se-containing vinyl frameworks). Thus, developing an effective catalytic methodology to introduce acetylene into fine chemicals providing diverse internal alkenes *via* 1,2-difunctionalization is highly desirable. However, exploiting gaseous acetylene to glue two components forming internal alkenes *via* 1,2-difunctionalization in a desired manner is not as easy as it might be expected due to the potential competition reactions between acetylene and alkene obtained from acetylene and the difficulty in controlling the regio- and stereoselectivity (Scheme 1b) [6a]. In particular, the high-energy vinyl radical intermediates obtained from radical addition to acetylene are highly unstable, have a short lifetime, and readily participate in different undesirable open-shell pathways. We questioned whether an appropriate bifunctional acetylene could give a valuable solution to this task. We have recently aimed to develop a

strategy to trap acetylene efficiently and convert it into a bifunctional and practical reagent while simultaneously exhibiting a rich reactivity profile. Ideally, this reagent should be readily prepared, stable, and easy to handle. As a leaving group, the sulfonyl moiety can controllably change the molecular polarity and activate reactive sites for further bond construction, especially for making carbon-carbon single and double bonds [20]. Notably, sulfone motifs are widely present in pharmaceutical molecules because they can control and balance the rate of drug metabolism and biotransformation [21]. Moreover, vinyl halides, especially vinyl bromide, have appeared as versatile substrates in a variety of chemical transformations [22]. Thus, β -bromo vinylsulfone would be an ideal bifunctional reagent that serves as an acetylene surrogate to connect two molecules rather than direct utilization of acetylene. Many strategies have been developed to access β -bromo vinylsulfone from substituted alkynes [23], but these methods have the disadvantages of using peroxide at high temperatures, requiring expensive and air-sensitive ligands/additives, and generating significant amounts of waste, which restrict their practical applications. Moreover, these developed approaches are limited to using electronically biased alkynes. Thus, the development of mild and efficient methods that introduce acetylene into sulfone motifs and bromide is of great significance. In this work, a general metal-free method is developed to quickly access a variety of (*E*)- β -bromo vinylsulfones using acetylene under mild conditions. The (*E*)- β -bromo vinylsulfones are bench-stable and can participate in different transformation reactions, such as Sonogashira coupling, Heck-type coupling, substituted reactions,

and desulfonylation transformations, offering numerous internal alkenes (Scheme 1c).

2 Experimental

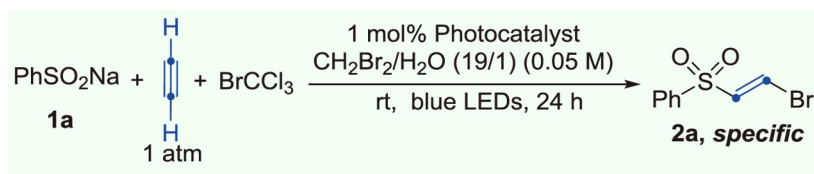
Experimental procedures and analytical data, nuclear magnetic resonance (NMR) spectra, and high-resolution mass spectrometry data are presented in the [Supporting Information online](#).

3 Results and discussion

3.1 Optimization of the reaction conditions

We started the study by using sodium sulfinate **1a** as the model substrate and CH_2Br_2 as both solvent and brominating reagent at room temperature under blue LED irradiation (Table 1, entry 1). To our delight, we obtained the target compound **2a** in 48% yield. A slight decrease in the yield was observed when the concentration was increased (Table 1, entry 2), suggesting that CH_2Br_2 might not be an efficient brominating agent. When BrCCl_3 (4 mL) was added to the reaction system, **2a** was produced in a 49% isolated yield (Table 1, entry 3). Then, we examined the amount of BrCCl_3 that may affect the transformation efficiency (Table 1, entries 4–7). Gratifyingly, the yield of **2a** could be greatly enhanced to 76% when BrCCl_3 was reduced to 0.2 mL (4 equiv.) (Table 1, entry 7). Further decreasing BrCCl_3 to 0.1 mL (2 equiv.) slightly decreased the yield to 66% (Table 1, entry 8). Importantly, a 77% isolated yield of **2a** could be accessed

Table 1 Reaction development for the preparation of β -halo vinylsulfones^{a)}



Entry	Photocatalyst	$\text{CH}_2\text{Br}_2/\text{BrCCl}_3$	Yield (%)
1 ^{b)}	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	—	48
2 ^{c)}	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	—	36
3	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	6 mL/4 mL	49
4	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	8 mL/2 mL	57
5	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	9 mL/1 mL	62
6	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	9.5 mL/0.5 mL	78
7	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	9.8 mL/0.2 mL	76
8	$\text{Ir}[\text{dF}(\text{CF}_3)\text{ppy}]_2(\text{phen})\text{PF}_6$	9.9 mL/0.1 mL	66
9 ^{d)}	4CzIPN	—	77

a) Reaction conditions: sodium sulfinate **1a** (0.5 mmol), photocatalyst (1 mol%), $\text{CH}_2\text{Br}_2/\text{BrCCl}_3$ (0.05 M), H_2O (0.5 mL), acetylene atmosphere (balloon, 1 atm), blue LEDs, rt, 24 h, isolated yield. *E/Z* > 20/1. b) CH_2Br_2 (0.03 M). c) CH_2Br_2 (0.1 M). d) BrCCl_3 (10 equiv.).

with a metal-free catalyst, 4CzIPN, in the presence of BrCCl_3 (10 equiv.) (Table 1, entry 9).

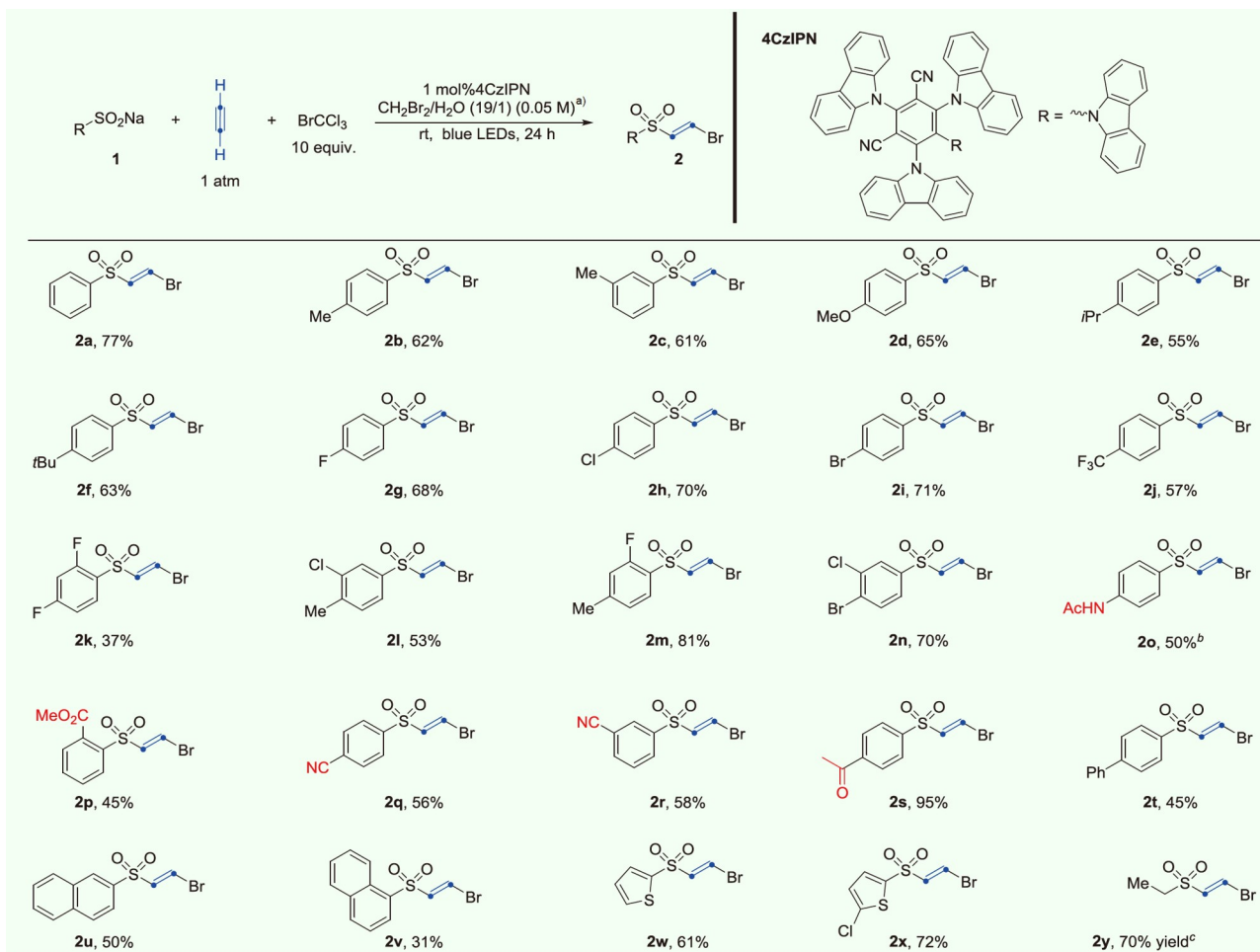
3.2 Substrate scope evaluation

Vinylsulfone-containing molecules have been found to be widespread in biological research [24], and β -bromo vinylsulfones are an important class of compounds that are versatile building blocks and valuable intermediates in organic synthesis and medicinal chemistry [25]. As a consequence, with the optimal reaction reactions in hand (Table 1, entry 9), we next investigated the scope of a variety of sodium sulfonates summarized in Scheme 2. A number of phenyl sodium sulfonates with electron-donating groups, including not only 1°-alkyl groups but also the more hindered 2°- and 3°-alkyl groups, were converted into their corresponding products in moderate to good yields (2a–2f). Relatively lower yields were found when an electron-withdrawing group was attached to the phenyl ring (2g–2k), which can be due to the reduced reductive quenching ability

toward the photoexcited photocatalyst. Gratifyingly, the reaction exhibited very good compatibility with various functional groups, including halides (2l–2n), amide (2o), ester (2p), nitrile (2q, 2r), and ketone (2s). Moreover, 2-naphthyl- and 1-naphthyl-substituted sodium sulfonates are both suitable substrates, although in slightly lower yields (2u, 2v). Notably, we also examined the heteroaryl-substituted sodium sulfonates and found that the corresponding products 2w and 2x were generated in good yields. Considering the good efficiencies of these transformations, we also extended the reaction scope to alkyl sodium sulfonates. Fortunately, the reaction went smoothly to afford 2y in good yield. It is worth noting that β -chloro and β -iodo vinylsulfones can also be furnished, although with lower efficiencies (See Supporting Information online for details).

3.3 Various transformations

The introduction of both bromide and the sulfonyl group at



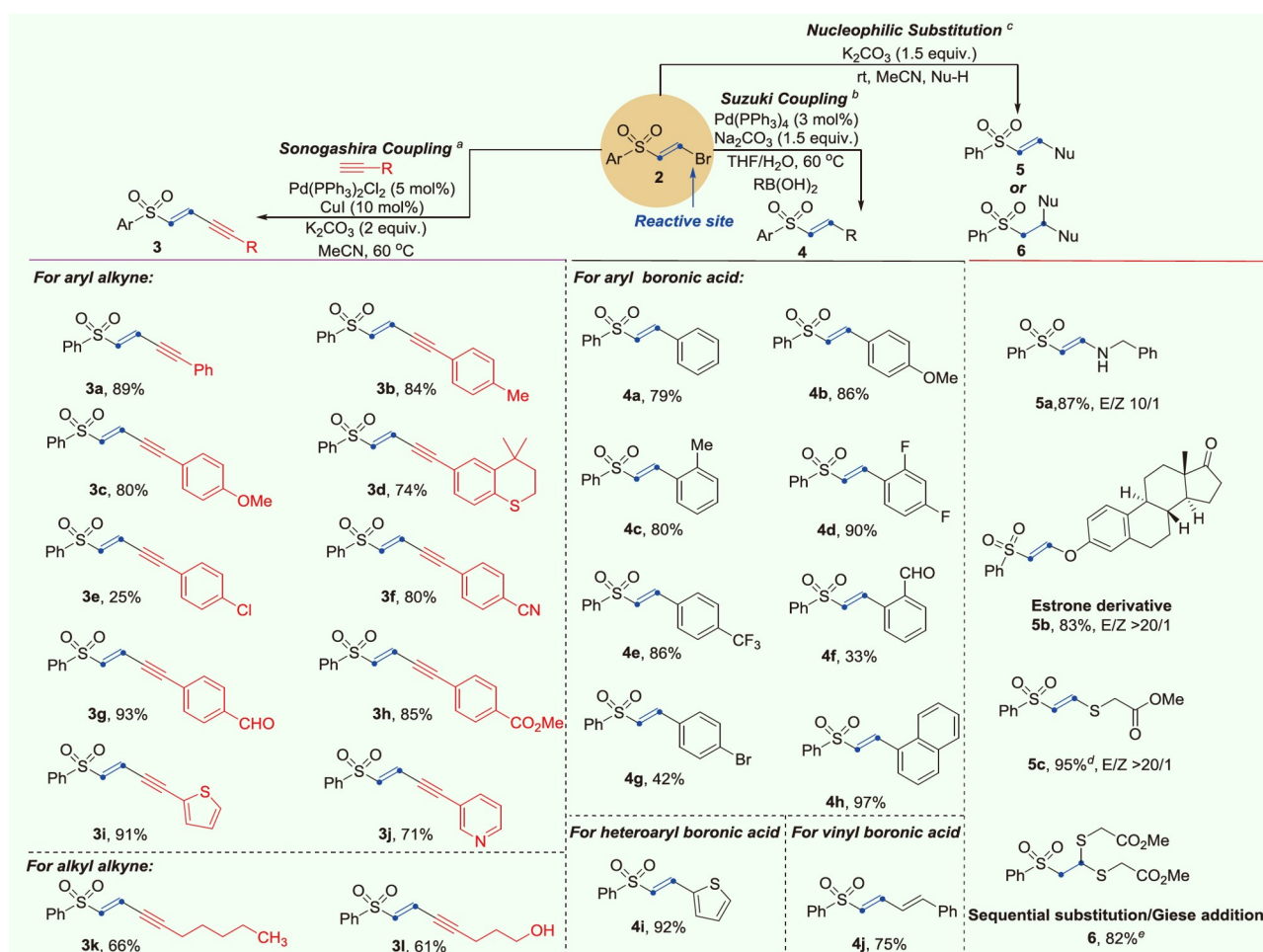
Scheme 2 Reaction scope of sodium sulfonates with acetylene. a) Reaction conditions: sodium sulfonate **1** (0.5 mmol), 4CzIPN (1 mol%), $\text{CH}_2\text{Br}_2/\text{H}_2\text{O}$ (19/1) (0.05 M), BrCCl_3 (10 equiv.), acetylene atmosphere (balloon, 1 atm), blue LEDs, rt, 24 h, isolated yield. $E/Z > 20/1$. b) $\text{MeCN}/\text{H}_2\text{O}$ (19/1) (0.05 M). c) NMR yield relative to starting material (color online).

the same time onto the triple bond affords the opportunity to design modular synthetic methods based on (*E*)- β -bromo vinylsulfone by further modifications on these functional groups. The compatibility and reactivity of (*E*)- β -bromo vinylsulfone in Sonogashira coupling were then analyzed by treatment of **2a** with various alkynes (Scheme 3, left). To our delight, a high yield of **3a** was obtained in the reaction of **2a** and phenylacetylene using similar published conditions [26]. Various aryl alkynes with different electronic properties worked well under these coupling conditions (**3b–3h**). Notably, the corresponding product **3e** could still be produced, although in lower yield, in the presence of a chloro group, which may be reactive in the Sonogashira coupling reaction conditions. Notably, functional groups such as nitrile (**3f**), aldehyde (**3g**), and ester (**3h**) were well tolerated. Also, thiophenyl and pyridinyl ethynes were suitable reaction partners in this transformation, giving **3i** and **3j** in 91% and 71% yields, respectively. The linear alkyl ethynes including functionalized alkyne could smoothly couple with **2a**, ob-

taining the corresponding ynylsulfonyl bromides **3k–3l** in good to excellent yields. These experimental results imply that acetylene can be introduced into the internal alkenes through coupling reactions of (*E*)- β -bromo vinylsulfone and alkynes.

In addition, these (*E*)- β -bromo vinylsulfone can also undergo Suzuki coupling with different boronic acids while maintaining the sulfonyl group intact to access vinylsulfonyl products (Scheme 3, middle). Phenylboronic acids with both electron-donating and electron-withdrawing groups on the phenyl ring are suitable substrates (**4a–4g**). The substrate containing a reactive group, *i.e.*, the chemically and biologically abundant aldehyde, gave the corresponding product **4f** in a relatively lower yield. The transformation of the 1-naphthyl derivative also gave the titled compound **4h** in 97% yield. Furthermore, *via* Suzuki couplings with alkenylboronic acids, the corresponding dienylyl sulfone molecule becomes accessible (**4j**).

Considering the abovementioned transformations based on



Scheme 3 Modular synthesis *via* transformations of (*E*)- β -bromo vinylsulfones **2**. a) **2** (0.3 mmol) in MeCN (3 mL), alkyne (0.45 mmol), K_2CO_3 (0.6 mmol), CuI (10 mol%), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (5 mol%) under a N_2 atmosphere, 60 °C. b) **2** (0.3 mmol) in tetrahydrofuran (THF) (3 mL), boronic acid (0.45 mmol), Na_2CO_3 (0.45 mmol), $\text{Pd}(\text{PPh}_3)_4$ (3 mol%) and H_2O (1 mL) under a N_2 atmosphere, 60 °C. c) **2** (0.2 mmol) in MeCN (2 mL), K_2CO_3 (0.3 mmol), Nu-H (0.3 mmol) under a N_2 atmosphere, room temperature. d) **2** (0.2 mmol), NuH (0.8 equiv.), K_2CO_3 (0.2 mmol). e) **2** (0.2 mmol), NuH (2.5 equiv.), K_2CO_3 (2.5 equiv.) (color online).

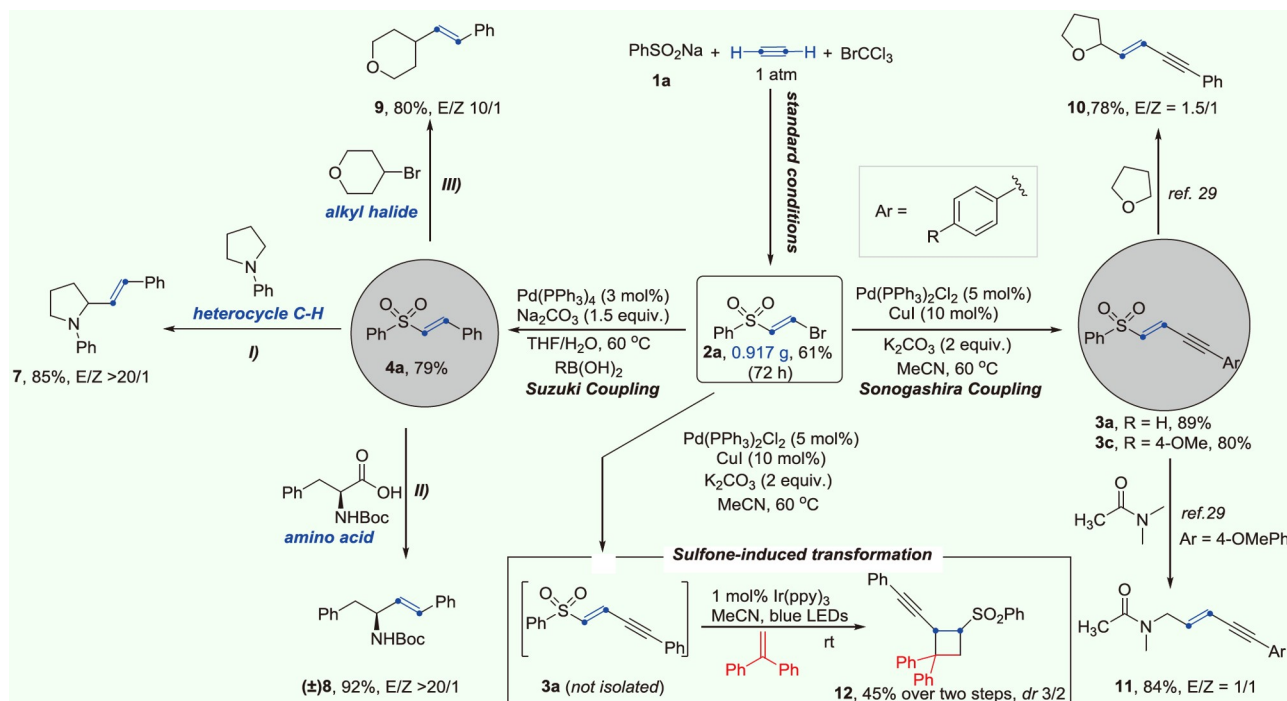
bromide, we questioned whether a nucleophilic substitution reaction was possible to access vinyl compounds. Vinylsulfone is a good Michael acceptor and has remarkable efficiency toward nucleophiles. Interestingly, selective substitutions of the bromide to give **5a** instead of Michael addition were observed when mixing the benzylamine with (*E*)- β -bromo vinylsulfone **2a**. Similar transformations were also found in the reaction of **2a** and other nucleophiles, such as phenol and thiol, giving **5b** and **5c** excellent yields and stereoselectivities. These results disclose the great potential of the structural modification of an array of complex biological molecules in medicinal chemistry. Notably, further increasing the thiol to 2.5 equiv., a double addition to **2a** took place, giving an expected mercaptal **6** in 82% yield. This transformation proceeded *via* nucleophilic substitution followed by Michael addition. These results indicate that the reactions can be controlled selectively to obtain vinyl product **5** and acetal **6** by adjusting the equivalents of nucleophiles. Moreover, this shows the potential for the incorporation of two different nucleophiles into the same carbon atom to obtain interesting molecules.

To further demonstrate the synthetic utility of this developed strategy, different experiments were performed (Scheme 4). A gram-scale experiment was performed, and **2a** was isolated in 61% yield, suggesting that large-scale production may be possible. Particularly, after the temporary modulation of chemical reactivity and desired functional

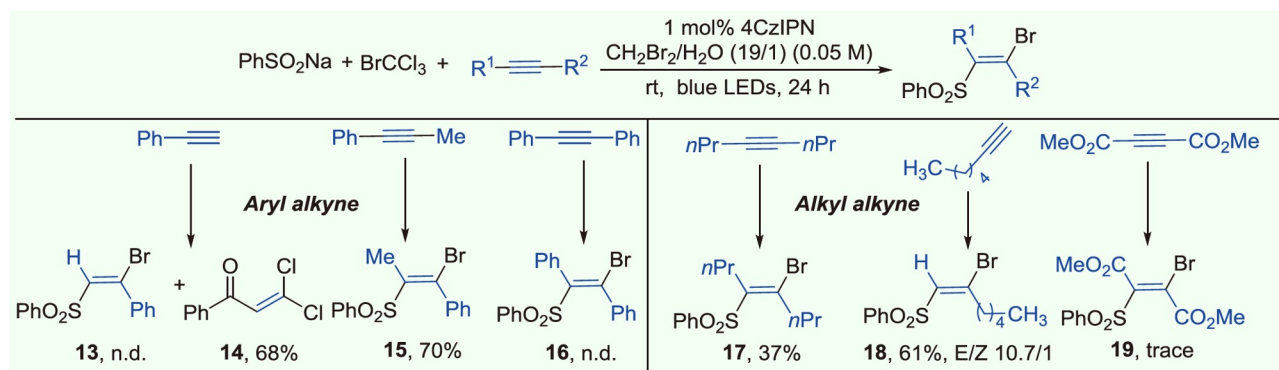
group transformation, the sulfonyl moiety can be easily removed. To some extent, radical-mediated desulfonylation processes have flourished rapidly along with the current renaissance of radical chemistry [20d]. Then, additional experiments were conducted to realize the transformations of the sulfonyl group (Scheme 4). Direct Csp³–H bond vinylation was obtained in the reaction of **4a** and 1-phenylpyrrolidine, affording **7** (*E/Z* >20/1) in 85% yield [27]. Due to the good performance obtained in this radical desulfonylation pathway and the extension of this approach, other kinds of radical precursors, such as amino acid and alkyl bromide, were next studied. It was found that this strategy can also be adapted for use with α -amino acid, affording the desired desulfonylated vinyl compound **8** (*E/Z* >20/1) in 90% yield. Alkyl bromide was also a suitable partner to access the corresponding product **9** (*E/Z* >20/1) in 80% yield [28]. Furthermore, based on previous work [29], similar products **10** and **11** could be obtained from **3a** *via* radical desulfonylation. It is worth noting that the substituted cyclobutene **12** can be prepared in 45% yield over two steps *via* the energy transfer strategy from **3a**, which was used directly without further purification.

3.4 Reactivity differences in different alkynes

As a surrogate of acetylene, functionalized acetylene (*E*)- β -bromo vinylsulfones exhibited powerful transformations,



Scheme 4 (Desulfonylation) transformations based on the sulfonyl group. Reaction conditions: I) **4a** (0.26 mmol), Ir[dF(CF₃)ppy]₂(dtbpy)PF₆ (0.003 mmol), CsOAc (0.75 mmol), 1-phenylpyrrolidine (0.63 mmol), 1,2-dichloroethane (DCE) (2.5 mL), blue LEDs, 24 h; II) **4a** (0.24 mmol), Ir(ppy)₂(dtbpy)PF₆ (0.003 mmol), *N*-tert-butoxycarbonyl-DL-phenylalanine (0.30 mmol) and CsHCO₃ (0.57 mmol), 1,4-dioxane (15 mL), blue LEDs, 24 h; III) **4a** (0.25 mmol), Ir[dF(CF₃)ppy]₂(dtbpy)PF₆ (0.003 mmol), K₂CO₃ (0.50 mmol), 4-bromotetrahydropyran (0.73 mmol), (TMS)₃SiH (0.30 mmol), MeCN (5 mL), blue LEDs, 24 h (color online).



Scheme 5 Reactivity differences between acetylene and its homologs (color online).

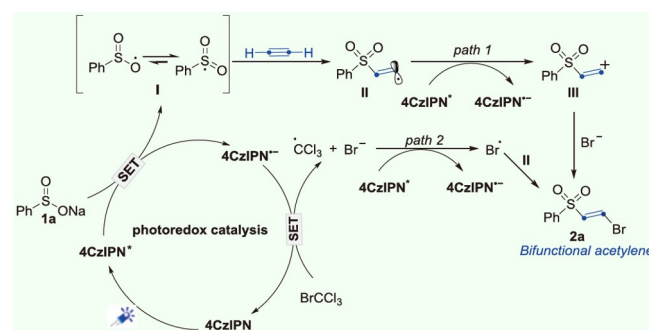
obtaining various functional molecules, especially alkenes. We wondered whether the established method for vinylsulfones is possible to produce substituted vinylsulfones when substituted alkynes are utilized. Then, different kinds of alkynes were subsequently examined (Scheme 5). The reaction of **1a** and phenylacetylene was performed under standard conditions, furnishing the interesting molecule **14** in 68% yield but without corresponding product **13** being observed. Further research on this fantastic transformation is ongoing in our lab. Notably, a 70% yield of (*E*)- β -bromo vinylsulfones **15** was isolated from 1-phenylpropyne, but no corresponding product **16** could be observed from diphenylacetylene. This phenomenon clearly exhibited a different reaction reactivity between substituted alkyne and acetylene and motivated us to test the reactivity of alkyl alkyne further. The vinylsulfones **17** and **18** were isolated in 37% and 61% yields from 4-octyne and 1-heptyne, respectively, *i.e.*, the alkyl alkyne shows a similar reactivity to acetylene. However, dimethyl acetylenedicarboxylate was not suitable for this transformation.

3.5 Reaction mechanism

To further gain mechanistic insights, several control experiments were performed. Control experiments demonstrated that blue LEDs and photocatalysts are essential to this transformation (for details, see the Supporting Information online). Moreover, the reaction was found to be inhibited by the addition of the radical scavenger TEMPO (for details, see the Supporting Information online), suggesting the involvement of radicals in the reaction. Our Stern–Volmer fluorescence experimental results show that the photoexcited 4CzIPN* is quenched by **1a**. Cyclic voltammetry measurements of BrCCl_3 revealed that the reduction potential of BrCCl_3 ($E_{1/2}^{\text{red}} = -0.766 \text{ V vs. SCE in MeCN}$) is higher than that of the reduced photocatalyst 4CzIPN^{•−} ($E[4\text{CzIPN}^{\text{•−}}/4\text{CzIPN}] = -1.21 \text{ V vs. SCE in MeCN}$) [30], which would lead to the photoreductive formation of the BrCCl_3 radical anion and then $\cdot\text{CCl}_3$ and Br^- (see Supporting Information

online for details). $\cdot\text{CCl}_3$ could undergo addition across unsaturated bonds, which is supported by the formation of **14** from phenylacetylene in Scheme 5. Moreover, the **14** adducts also demonstrated the generation of the vinyl cation and involvement of nucleophilic reaction (see Supporting Information online for details), which agrees with the results of common alkynes in Scheme 5. CH_2Br_2 cannot be reduced by 4CzIPN^{•−} due to its stronger reduction potential ($E_{1/2}^{\text{red}} = -2.073 \text{ V vs. SCE in MeCN}$).

Based on the mechanistic results and known literature [31], a plausible reaction mechanism is illustrated in Scheme 6. Upon irradiation with visible light, the photocatalyst 4CzIPN is known to access the highly oxidizing excited state species (4CzIPN*), which can be reductively quenched by sodium sulfinate **1a** to furnish radical intermediate **I** and reduced photocatalyst 4CzIPN^{•−}. The single electron transfer between the 4CzIPN^{•−} and BrCCl_3 generates $\cdot\text{CCl}_3$ and a bromine anion together with regeneration of the photocatalyst 4CzIPN. Then, the intermediate **I** $\text{PhSO}_2\cdot$ can be captured by acetylene gas to obtain vinyl radical species **II**, which is then photooxidized to afford cation intermediate **III**, followed by nucleophilic reaction with Br^- to afford the final product **2a** (path 1). Moreover, in path 2, the vinyl radical intermediate **II** undergoes radical cross-coupling of the Br^\cdot radical [31d–31f] from the bromine anion oxidized by 4CzIPN* [31d,31f] to generate the β -bromo vinyl sulfone adduct, which cannot be excluded.



Scheme 6 Plausible mechanism (color online).

4 Conclusions

In this work, we have designed a general approach to incorporating gaseous acetylene into a bench-stable and practical reagent, (*E*)- β -bromo vinylsulfones, which can serve as acetylene surrogates to realize different transformations with high efficiency. Sonogashira coupling, Suzuki coupling, and substitution with different *N*-, *O*-, and *S*-nucleophiles by manipulations on the β -bromide position can be well established while maintaining the sulfonyl group intact. The sulfonyl group involved in (*E*)- β -bromo vinylsulfones can also be converted to various alkenes with different partners, such as alkyl amine, α -amino acid, alkyl halide, and ethers. These powerful transformations of (*E*)- β -bromo vinylsulfones based on both sulfonyl group and bromide and their simple preparation from acetylene will promote the utilization of acetylene in organic synthesis.

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Conflict of interest The authors declare no conflict of interest.

Supporting information The supporting information is available online at chem.scichina.com and link.springer.com/journal/11426. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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Visible Light-Promoted Three-Component Carboazidation of Unactivated Alkenes with TMSN_3 and Acrylonitrile[†]

Bo Yang,^{‡,a} Xiang Ren,^{‡,a} Xuzhong Shen,^a Tongtong Li,^a and Zhan Lu^{*,a}

ABSTRACT A novel difunctionalization of unactivated alkenes has been reported via visible light-promoted three-component carboazidation using TMSN_3 and acrylonitrile as partners without any stoichiometric oxidants. This protocol is operationally simple for straightforward access to azido derivatives with good functional group tolerance from readily available starting materials. A facile azido radical-catalyzed [3+2] cycloaddition reaction of vinylcyclopropane with acrylonitrile was also observed to deliver a multi-substituted cyclopentane.

KEYWORDS alkene difunctionalization, visible light photocatalysis, three-component reaction, redox-neutral, organoazide, azidyl radical

Introduction

Alkene difunctionalizations have been continuously attractive for efficient construction of various useful synthetic intermediates and targets.^[1] Organoazides have been used as efficient synthetic intermediates due to their diversity of further transformations.^[2] The combination of the formations of carbon-azide bond and carbon-X (halogen, P, O, N) bonds has been successfully reported.^[3] The carboazidation of alkenes was used to form carbon-(sp or sp²) carbon bonds or fluorinated carbon bonds.^[4] However, to the best of our knowledge, the three-component carboazidation reaction with the formation of non-fluorinated carbon (sp³)-carbon (sp³) is still limited (Scheme 1). Renaud and co-workers reported two types of carboazidation of alkenes with α -iodoacetate and phenylsulfonyl azide, or using alkylsulfonyl azides as both alkyl and azido sources.^[5] Recently, Zhu^[6] group and Yang^[7] group, respectively, reported carboazidation of terminal styrenes or cyclic styrene with acetonitrile or aldehydes as carbon sources using peroxides as oxidants. Li and co-workers reported an azidomethylation of active alkenes with dimethyl sulfoxide as a methyl source using H_2O_2 as an oxidant.^[8] So far, over stoichiometric peroxides have to be used and aliphatic alkene is a still challenging

substrate. Here, we reported a three-component carboazidation of unactivated alkenes with TMSN_3 and acrylonitrile via visible light photocatalysis without any stoichiometric oxidants.

Our group is quite interested in visible light-promoted alkene difunctionalizations.^[9] In our previous studies, the azido radical^[10] could react with alkene to form carbon radical,^[11] which could be trapped by dioxygen.^[9e] Based on these result, we hypothesized that the Michael acceptor, such as acrylonitrile, was an alternative trapper which leads to the formation of carbon (sp³)-carbon (sp³) bond to afford the carboazidation product (Scheme 1b).

The proposed mechanism was presented in Scheme 1c. The azidotrimethylsilane could be oxidized by iridium photocatalyst ($E_{\text{Ir}^{IV}/\text{Ir}^{III}} = +0.66 \text{ V}$)^[12] to azido radical based on the oxidation potential of the azidotrimethylsilane (measured 0.66 V vs. SCE in MeCN and 0.600 V vs. SCE in acetone) or azido anion (0.655 V vs. SCE in MeCN).^[13]

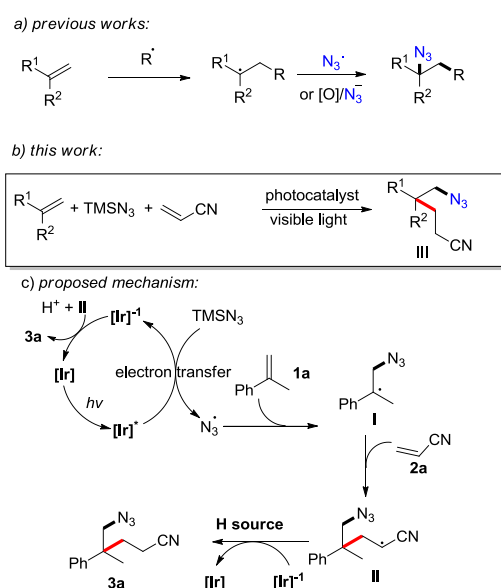
The azido radical could be trapped by alkene to generate benzyl radical species I, which could undergo radical Michael addition to form carbon center radical II. This carbon radical II could be reduced by low valent photocatalyst to regenerate the ground state of photocatalyst, and afford the corresponding product **3a** in the presence of proton source.

Results and Discussion

Based on the above hypothesis, we extensively investigated the reaction conditions for the carboazidation of α -methyl styrene with various photocatalyst at room temperature under the irradiation of 8 W blue LEDs for 9 h using water as proton donor and acetonitrile as a solvent. Various visible light photocatalysts were screened using TMSN_3 as an azido source and acrylonitrile as a Michael acceptor, and $\text{Ir}(\text{ppy})_2(\text{dtbbpy})\text{PF}_6$ was found to catalyze the reaction to afford three-component carboazidation product in 67% yield (entry 1, Table 1 and also in Table S1). It should be noted that the generated azido radical could react much rapidly with α -methyl styrene than electron-deficient acrylonitrile. Various solvents were tested and no better results were observed (entries 2–7). The reaction with 2 equiv. of TMSN_3 in a solvent of MeCN (0.2 mol/L) afforded the desired product in 80% yield (entry 8 as the standard conditions A). No desired products were obtained in the absence of photocatalyst or light (entries 10 and 11). Additionally, the reaction took place by using MeOH (3 equiv.) instead of H_2O (10 equiv.) to give **3a** in 71% yield (entry 12 as the standard conditions B).

With optimized conditions in hands, the scope of substrate was explored (Table 2). The α -methyl styrenes with various

Scheme 1 The carboazidation of alkenes



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[‡] B. Yang and X. Ren are contributed equally to this work.

[†] Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday.

Table 1 Conditions optimization for carboazidation of alkenes^a

Entry	Changes to	Yield ^b /%
1	—	67
2	THF	57
3	MeOH	0
4	DCM	21
5	Acetone	61
6	MeNO ₂	17
7	dioxane	61
8	TMSN ₃ (2 equiv.), 0.2 mol/L	80 (75)
9	TMSN ₃ (2 equiv.), 0.2 mol/L without water	67
10	entry 8 without photocatalyst	0
11	entry 8 without light	0
12	TMSN ₃ (2 equiv.), acetone (0.2 mol/L), MeOH (3 equiv.) was used instead of H ₂ O	71 (70)

^a Conditions: α -methyl styrene (0.3 mmol), TMSN₃ (3 equiv.), acrylonitrile (6 equiv.), water (10 equiv.), Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), solvent (0.1 mol/L), at room temperature under the irradiation of 8 W blue LEDs for 9 h. ^b Yields were determined by ¹H NMR analysis using mesitylene as an internal standard. Isolated yield in the parentheses.

substituents, such as ether, halides, amine, amide, at *para*- or *meta*- position on aryl ring were suitable for this transformation. However, the sterically hindered substrates with *ortho*-substitution could not afford the desired product. The α -1°-alkyl substituent could be tolerated (**3k–3l**), however, the α -2°-alkyl substituent was not suitable (**3m**). The simple styrenes with electron-rich or electron-deficient substitutions could be transferred to the corresponding carboazidation products in 58%–79% yields. The aliphatic alkenes could participate in reactions to afford **3u** and **3v** in 62% and 47% yield, respectively. The acyl protected cinnamyl alcohol could be delivered to **3w** in 37% yield with poor diastereoselectivity. The trisubstituted alkene could also involve in the reaction to give **3x** in 45% yield with 3.9/1 *dr*. The alkene containing estrone-derivative could be transformed into the corresponding product. The intramolecular reaction of 1,6-diene **4** could undergo smoothly to afford cyclization product **5** in 62% yield with 3.2/1 *dr* (Table 2 eq. 1). The other Michael acceptors have been tested. The reaction of styrene with diethyl fumarate afforded **3aa** in 21% yield with 2/1 *dr*. The reaction of styrene with cyclohex-2-enone afforded **3ab** in 34% yield with 1/1 *dr*. While the reaction of styrene with diethyl 2-methylenemalonate did not afford desired product **3ac**.

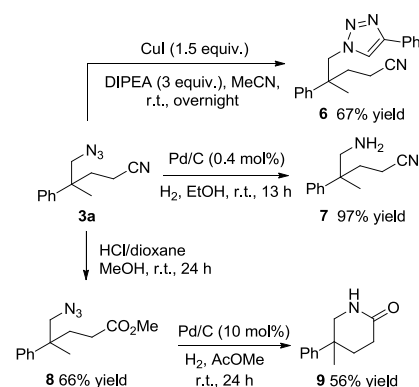
To demonstrate the synthetic utility, the further derivatizations have been carried out (Scheme 2). The click reaction of **3a** afforded **6** in 67% yield. The reduction reaction of **3a** could afford **7** in 97% yield. The nitrile group could be hydrolyzed to give **8** in 66% yield, with the recovery of **3a** for 25%. The lactam **9** could be obtained via reduction and cyclization of **8** using 10 mol% Pd/C under one atmosphere of hydrogen in 56% yield.

The reactions were inhibited in the presence of TEMPO or air which demonstrated the possibility of radical process (eqs. 2 and 3). The reaction of **1a** using D₂O afforded **D-3a** in 68% yield with 45% D-incorporation, which indicated that the H₂O was the hydrogen donor (eq. 4). We also carried out the fluorescence quenching study, and found that the fluorescence of photocatalyst could be quenched by TMSN₃, which was consistent with our hypothesis (See SI Figure S3). The reaction of radical-clock substrate **10** under the standard conditions did not afford any carboazidation or ring-opening carboazidation products (eq. 4). Unexpectedly, a facile azido radical initiated [3+2] cycloaddition reaction of **10**

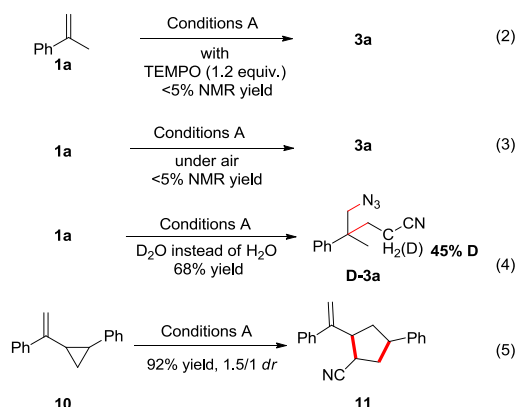
Table 2 Substrate scope

Intermolecular carboazidation		
3b : R = 3-OMe, 62% ^a	3f : R = 4-Cl, 59% ^a	
3c : R = 4-Me, 54% ^b	3g : R = 3-Cl, 67% ^b	
3d : R = 3-Me, 60% ^a	3h : R = 4-F, 79% ^a	
3e : R = 2-Me, trace ^a	3i : R = 3-NH ₂ , 52% ^a	
	3j : R = 4-NHBoc, 44% ^b	
3k : R = Et, 60% ^b		
3l : R = <i>n</i> Pr, 49% ^a		
3m : R = <i>i</i> Pr, trace ^a		
3n : 45% ^a		
3o : R = H, 80% ^b		
3p : R = 4-Me, 58% ^a		
3q : R = 4-OMe, 59% ^b		
3r : R = 3-Cl, 73% ^b		
3s : R = 3-MeO-4-F, 79% ^b		
3t : 32% ^b		
3u : 62% ^b	3v : 47% ^b	3w : 37% ^b , 1.1/1 <i>dr</i>
3x : 45% ^b , 3.9/1 <i>dr</i>	3y : 40% ^b N.D. <i>dr</i>	
Intramolecular carboazidation		
4 : E/Z 3.3/1	5 : 62%, 3.2/1 <i>dr</i>	
Intermolecular carboazidation with different Michael acceptors		
3aa : 21% ^b , <i>dr</i> 2/1	3ab : 34% ^b , <i>dr</i> 1/1	3ac : trace ^b

^a Conditions A: Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), MeCN (0.2 mol/L), alkene (0.3 mmol), Michael acceptor (6.0 equiv.), TMSN₃ (2 equiv.), H₂O (10 equiv.), r.t., 8 W blue LEDs. ^b Conditions B: Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), acetone (0.2 mol/L), alkene (0.3 mmol), Michael acceptor (6.0 equiv.), TMSN₃ (2 equiv.), MeOH (3 equiv.), r.t., 8 W blue LEDs.

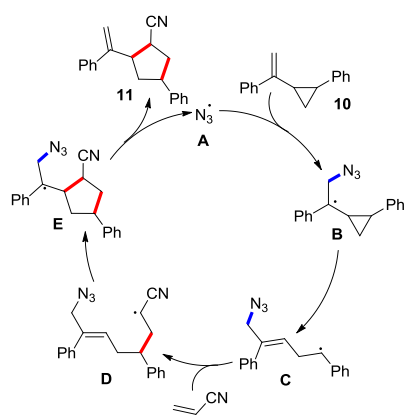
Scheme 2 Further derivatizations

with acrylonitrile was observed to deliver a substituted cyclo-



pentane **11** in 92% yield (major isomer/other minor isomers 1.5/1). The reaction of **10** without TMSN₃ did not occur. To the best of our knowledge, it is the first case of nitrogen radical-promoted [3+2] cycloaddition of vinylcyclopropane with alkene. These results also strongly supported the radical pathway. We proposed that the generated azido radical could attack carbon-carbon double bond on the VCP to afford the benzyl radical species (**B**), which could lead to a radical ring opening pathway and generate carbon center radical (**C**). The radical **C** could be trapped by acrylonitrile to afford radical species **D**, which underwent the intramolecular cyclization to afford **E**. The deazidation reaction of **E** could occur to afford **11** and regenerate the azido radical. The control experiments have been added in SI.

Scheme 3 Possible mechanism of the formation of compound **11**



Conclusions

In summary, we reported the first example of visible light-promoted three-component carboazidation of unactivated alkenes using TMSN₃ and acrylonitrile as reaction partners without any stoichiometric peroxides. The intramolecular reaction of 1,6-diene could also undergo smoothly to afford the cyclization product. The reaction afforded δ -azido alkylnitriles, which could be readily converted into valuable building blocks for medicinal chemistry and organic synthesis. A facile azido radical initiated [3+2] cycloaddition reaction of vinylcyclopropane with acrylonitrile was observed to deliver a substituted cyclopentane. The asymmetric alkene difunctionalization is undergoing in our laboratory.

Experimental

General Information. DCM, MeCN, NEt₃ and *i*Pr₂NEt were distilled from calcium hydride, and acetone was distilled from potassium carbonate. Ethanol methanol and methyl acetate were used

directly. Unless otherwise noted, all the corresponding ketones from suppliers were used directly without further purification. Azidotrimethylsilane (TMSN₃) was purchased from J&K Chemicals. Acrylonitrile was purchased from Aladdin and used directly. NMR spectra were recorded on a Bruker-400 instrument. ¹H NMR chemical shifts were referenced to the tetramethylsilane (δ 0), ¹³C NMR chemical shifts were referenced to the solvent resonance (δ 77.00, CDCl₃). The following abbreviations (or combinations thereof) were used to explain multiplicities: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad, q=quadruplet. IR spectra were recorded on a Perkin-Elmer Spectrum One FTIR spectrometer with diamond ATR accessory. High-resolution mass spectra (HRMS) were recorded on Waters XEVOG2-S TOF or GCT Premier. All manipulations were conducted under Schlenk tubes.

General procedure A: Conditions A. To a 50 mL flame-dried Schlenk flask cooled under N₂, Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), alkene **1** (0.3 mmol), TMSN₃ (0.6 mmol), acrylonitrile (120 μ L), H₂O (10 equiv.) and acetonitrile (1.5 mL) were added. The mixture was degassed through three freeze-pump-thaw cycles under N₂. The reaction was placed at room temperature and stirred in the front of 8 W blue LEDs at a distance of 10 cm for 9 h. The reaction mixture was concentrated *in vacuo* before it was purified by flash chromatography on silica gel to afford **3**.

General procedure B: Conditions B. To a 50 mL flame-dried Schlenk flask cooled under N₂, Ir(ppy)₂(dtbbpy)PF₆ (2 mol%), alkene **1** (0.3 mmol), TMSN₃ (0.6 mmol), acrylonitrile (120 μ L), MeOH (3 equiv.) and acetone (1.5 mL) were added. The mixture was degassed through three freeze-pump-thaw cycles under N₂. The reaction was placed at room temperature and stirred in the front of 8 W blue LEDs at a distance of 10 cm for 9 h. The reaction mixture was concentrated *in vacuo* before it was purified by flash chromatography on silica gel to afford **3**.

5-Azido-4-methyl-4-phenylpentanenitrile (3a). Prepared according to the general procedure A using alkene **1a** (34.9 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3a** (47.5 mg, 0.22 mmol, 75% yield) as a colorless oil. IR ν : 2973, 2922, 2246, 2100, 1493, 1254, 1052 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.42–7.34 (m, 2H), 7.33–7.25 (m, 3H), 3.51 (d, *J*=12.0 Hz, 1H), 3.44 (d, *J*=12.0 Hz, 1H), 2.28–1.94 (m, 4H), 1.42 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 141.7, 128.9, 127.3, 126.1, 119.6, 62.2, 42.2, 34.9, 21.9, 12.4; HRMS (ESI-TOF) Calcd for C₁₂H₁₄N₄ [M+H]⁺: 215.1297; found 215.1303.

5-Azido-4-(3-methoxyphenyl)-4-methylpentanenitrile (3b). Prepared according to the general procedure A using alkene **1b** (42.5 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3b** (43.3 mg, 0.18 mmol, 62% yield) as a colorless oil. IR ν : 2973, 2903, 2248, 2101, 1583, 1248, 1049 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.34–7.27 (m, 1H), 6.89–6.78 (m, 3H), 3.82 (s, 3H), 3.50 (d, *J*=12.0 Hz, 1H), 3.43 (d, *J*=12.0 Hz, 1H), 2.25–1.94 (m, 4H), 1.40 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 159.9, 143.5, 129.9, 119.7, 118.3, 113.2, 111.5, 62.2, 55.2, 42.3, 35.0, 21.9, 12.4; HRMS (ESI-TOF) Calcd for C₁₃H₁₆N₄O [M+Na]⁺: 267.1222; found 267.1228.

5-Azido-4-methyl-4-(*p*-tolyl)pentanenitrile (3c). Prepared according to the general procedure B using alkene **1c** (38.6 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3c** (36.3 mg, 0.16 mmol, 54% yield) as a colorless oil. IR ν : 2973, 2904, 2247, 2100, 1515, 1385, 1256, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.23–7.11 (m, 4H), 3.49 (d, *J*=12.0 Hz, 1H), 3.42 (d, *J*=12.0 Hz, 1H), 2.34 (s, 3H), 2.25–1.93 (m, 4H), 1.40 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 138.6, 137.0, 129.6, 126.0, 119.8, 62.4, 42.0, 34.9, 22.0, 20.9, 12.4; HRMS (ESI-TOF) Calcd for C₁₃H₁₆N₄ [M+H]⁺: 229.1453; found 229.1457.

5-Azido-4-methyl-4-(*m*-tolyl)pentanenitrile (3d). Prepared

according to the general procedure A using alkene **1d** (39.8 mg, 0.30 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3d** (41.5 mg, 0.18 mmol, 60% yield) as a colorless oil. IR ν : 2973, 2904, 2100, 2247, 1452, 1385, 1051 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.30–7.22 (m, 1H), 7.13–7.03 (m, 3H), 3.50 (d, J =12.0 Hz, 1H), 3.43 (d, J =12.0 Hz, 1H), 2.37 (s, 3H), 2.24–1.94 (m, 4H), 1.40 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 141.7, 138.5, 128.7, 128.0, 126.8, 123.1, 119.7, 62.3, 42.1, 34.9, 21.9, 21.6, 12.4; HRMS (ESI-TOF) Calcd for C₁₃H₁₆N₄ [M+H]⁺: 229.1453; found 229.1452.

5-Azido-4-(4-chlorophenyl)-4-methylpentanenitrile (3f). Prepared according to the general procedure A using alkene **1f** (47.4 mg, 0.31 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3f** (45.3 mg, 0.18 mmol, 59% yield) as a colorless oil. IR ν : 2973, 2903, 2250, 2102, 1401, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.36 (d, J =8.4 Hz, 2H), 7.23 (d, J =8.8 Hz, 2H), 3.50 (d, J =12.0 Hz, 1H), 3.43 (d, J =12.0 Hz, 1H), 2.24–1.97 (m, 4H), 1.41 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 140.4, 133.3, 129.1, 127.6, 119.4, 62.1, 42.0, 34.8, 22.0, 12.4; HRMS (ESI-TOF) Calcd for C₁₂H₁₃ClN₄ [M+H]⁺: 249.0907; found 249.0921.

5-Azido-4-(3-chlorophenyl)-4-methylpentanenitrile (3g). Prepared according to the general procedure B using alkene **1g** (44.8 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3g** (48.9 mg, 0.20 mmol, 67% yield) as a colorless oil. IR ν : 2977, 2903, 2248, 2102, 1570, 1407, 1074 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.36–7.25 (m, 3H), 7.21–7.16 (m, 1H), 3.51 (d, J =12.0 Hz, 1H), 3.44 (d, J =12.0 Hz, 1H), 2.24–1.98 (m, 4H), 1.42 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 144.1, 135.0, 130.2, 127.6, 126.6, 124.3, 119.4, 61.9, 42.4, 34.8, 21.9, 12.4; HRMS (ESI-TOF) Calcd for C₁₂H₁₃ClN₄ [M+H]⁺: 249.0907; found 249.0919.

5-Azido-4-(4-fluorophenyl)-4-methylpentanenitrile (3h). Prepared according to the general procedure A using alkene **1h** (42.9 mg, 0.31 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3h** (57.7 mg, 0.25 mmol, 79% yield) as a colorless oil. IR ν : 2982, 2903, 2252, 2104, 1512, 1235, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.26 (dd, J =7.6, 5.6 Hz, 2H), 7.07 (t, J =8.4 Hz, 2H), 3.49 (d, J =12.0 Hz, 1H), 3.42 (d, J =12.0 Hz, 1H), 2.24–1.93 (m, 4H), 1.41 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 161.8, (d, J =246 Hz), 137.5 (d, J =3.3 Hz), 127.8 (d, J =8.0 Hz), 119.5, 115.7 (d, J =21.1 Hz), 62.3, 41.9, 34.9, 22.0, 12.3; ¹⁹F NMR (376 MHz, CDCl₃) δ : -115.0; HRMS (ESI-TOF) Calcd for C₁₂H₁₃FN₄ [M+H]⁺: 233.1202; found 232.1205.

4-(3-Aminophenyl)-5-azido-4-methylpentanenitrile (3i). Prepared according to the general procedure A using alkene **1i** (42.2 mg, 0.36 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3i** (37.7 mg, 0.16 mmol, 52% yield) as a colorless oil. IR ν : 2973, 2904, 2247, 2100, 1606, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.14 (dd, J =8.0, 7.6 Hz, 1H), 6.64 (dd, J =8.0, 1.2 Hz, 1H), 6.62–6.54 (m, 2H), 3.72 (br s, 2H), 3.47 (d, J =12.4 Hz, 1H), 3.40 (d, J =12.4 Hz, 1H), 2.21–1.89 (m, 4H), 1.36 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 146.8, 143.0, 129.8, 119.8, 116.1, 114.0, 112.8, 60.2, 42.2, 34.9, 21.9, 12.4; HRMS (ESI-TOF) Calcd for C₁₂H₁₅N₅ [M+K]⁺: 268.0965; found 268.0952.

tert-Butyl 4-(1-azido-4-cyano-2-methylbutan-2-yl)phenylcarbamate (3j). Prepared according to the general procedure B using alkene **1j** (72.6 mg, 0.31 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3j** (50.8 mg, 0.15 mmol, 44% yield) as a colorless oil. IR ν : 3340, 2981, 2903, 2250, 2102, 1716, 1525 1407 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.38 (d, J =8.4 Hz, 2H), 7.19 (d, J =8.4 Hz, 2H), 6.57 (br s, 1H), 3.47 (d, J =12.4 Hz,

1H), 3.41 (d, J =12.4 Hz, 1H), 2.23–1.93 (m, 4H), 1.52 (s, 9 H), 1.39 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 152.6, 137.5, 136.1, 126.7, 119.7, 118.8, 80.7, 62.3, 41.9, 34.9, 28.3, 21.9, 12.4; HRMS (ESI-TOF) Calcd for C₁₇H₂₃N₅O₂ [M+Na]⁺: 352.1749; found 352.1759.

4-(Azidomethyl)-4-phenylheptanenitrile (3k). Prepared according to the general procedure B using alkene **1k** (37.2 mg, 0.28 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3k** (38.3 mg, 0.17 mmol, 60% yield) as a colorless oil. IR ν : 2973, 2247, 2103, 1452 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.40–7.35 (m, 2H), 7.30–7.25 (m, 1H), 7.23–7.20 (m, 2H), 3.70 (d, J =12.4 Hz, 1H), 3.65 (d, J =12.4 Hz, 1H), 2.16–2.02 (m, 4H), 1.83–1.76 (m, 2H), 0.75 (t, J =7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 141.4, 128.9, 127.1, 126.1, 119.7, 55.8, 44.7, 32.6, 28.7, 12.2, 7.9; HRMS (ESI-TOF) Calcd for C₁₃H₁₆N₄ [M+H]⁺: 229.1448; found 229.1450.

4-(Azidomethyl)-4-phenylheptanenitrile (3l). Prepared according to the general procedure A using alkene **1l** (40.4 mg, 0.28 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3l** (35.5 mg, 0.15 mmol, 53% yield) as a colorless oil. IR ν : 2961, 2248, 2101, 1460 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.37 (dd, J =8.0, 7.2 Hz, 2H), 7.30–7.26 (m, 1H), 7.24–7.19 (m, 2H), 3.69 (d, J =12.4 Hz, 1H), 3.64 (d, J =12.4 Hz, 1H), 2.21–1.97 (m, 4H), 1.75–1.64 (m, 2H), 1.24–0.98 (m, 2H), 0.89 (t, J =7.2 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 141.7, 128.9, 127.1, 126.0, 119.7, 56.2, 44.5, 38.6, 32.9, 16.7, 14.4, 12.2; HRMS (ESI-TOF) Calcd for C₁₄H₁₈N₄ [M+H]⁺: 243.1610; found 234.1611.

3-(1-(Azidomethyl)-2,3-dihydro-1H-inden-1-yl)propanenitrile (3n). Prepared according to the general procedure A using alkene **1n** (42.1 mg, 0.32 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3n** (32.6 mg, 0.14 mmol, 45% yield) as a colorless oil. IR ν : 2925, 2246, 2099, 1452, 1264 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.29–7.20 (m, 3H), 7.17–7.10 (m, 1H), 3.48 (d, J =12.0 Hz, 1H), 3.44 (d, J =12.0 Hz, 1H), 3.05–2.85 (m, 2H), 2.34–1.92 (m, 6H); ¹³C NMR (101 MHz, CDCl₃) δ : 143.9, 143.7, 128.1, 126.9, 125.3, 123.2, 119.7, 59.4, 51.6, 33.4, 32.5, 30.1, 12.7; HRMS (ESI-TOF) Calcd for C₁₃H₁₄N₄ [M+H]⁺: 227.1297; found 227.1300.

5-Azido-4-phenylpentanenitrile (3o). Prepared according to the general procedure B using alkene **1o** (35.0 mg, 0.34 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3o** (54.1 mg, 0.27 mmol, 80% yield) as a colorless oil. IR ν : 2923, 2247, 2099, 1454, 1263 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.43–7.27 (m, 3H), 7.21 (d, J =7.6 Hz, 2H), 3.57 (dd, J =12.0, 6.8 Hz, 1H), 3.48 (dd, J =12.0, 6.8 Hz, 1H), 3.02–2.91 (m, 1H), 2.33–2.03 (m, 3H), 1.99–1.86 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ : 139.1, 129.1, 127.9, 127.6, 119.0, 56.4, 44.7, 28.6, 15.1; HRMS (ESI-TOF) Calcd for C₁₁H₁₂N₄ [M+H]⁺: 201.1140; found 201.1141.

5-Azido-4-(*p*-tolyl)pentanenitrile (3p). Prepared according to the general procedure A using alkene **1p** (36.1 mg, 0.30 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H₂O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **3p** (37.9 mg, 0.18 mmol, 58 % yield) as a colorless oil. IR ν : 2925, 2247, 2098, 1515, 1266 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.18 (d, J =7.6 Hz, 2H), 7.09 (d, J =7.6 Hz, 2H), 3.54 (dd, J =12.0, 6.8 Hz, 1H), 3.45 (dd, J =12.4, 7.2 Hz, 1H), 2.98–2.86 (m, 1H), 2.34 (s, 3H), 2.31–2.04 (m, 3H), 1.96–1.82 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ : 137.6, 136.0, 129.8, 127.4, 119.1, 56.5, 44.3, 28.7, 21.0, 15.1; HRMS (ESI-TOF) Calcd for C₁₂H₁₄N₄ [M+H]⁺: 215.1297; found 215.1300.

5-Azido-4-(4-methoxyphenyl)pentanenitrile (3q). Prepared according to the general procedure B using alkene **1q** (39.7 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting

materials to afford **3q** (39.9 mg, 0.17 mmol, 59% yield) as a colorless oil. IR ν : 2976, 2903, 2250, 2100, 1513, 1250, 1051 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.12 (d, J =8.8 Hz, 2H), 6.90 (d, J =8.8 Hz, 2H), 3.80 (s, 3H), 3.52 (dd, J =12.4, 6.8 Hz, 1H), 3.44 (dd, J =12.4, 7.2 Hz, 1H), 2.97–2.85 (m, 1H), 2.32–2.04 (m, 3H), 1.94–1.81 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ : 159.1, 131.0, 128.6, 119.1, 114.5, 56.7, 55.2, 43.9, 28.8, 15.1; HRMS (ESI-TOF) Calcd for C₁₂H₁₄N₄O [M+H]⁺: 231.1246; found 231.1254.

5-Azido-4-(3-chlorophenyl)pentanenitrile (3r). Prepared according to the general procedure B using alkene **1r** (46.3 mg, 0.33 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3r** (57.0 mg, 0.24 mmol, 73% yield) as a colorless oil. IR ν : 2973, 2903, 2247, 2098, 1408, 1073 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.35–7.27 (m, 2H), 7.21 (s, 1H), 7.15–7.08 (m, 1H), 3.56 (dd, J =12.4, 6.8 Hz, 1H), 3.49 (dd, J =12.4, 6.8 Hz, 1H), 3.01–2.90 (m, 1H), 2.36–2.24 (m, 1H), 2.23–2.06 (m, 2H), 1.99–1.84 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ : 141.4, 135.0, 130.4, 128.1, 127.7, 126.0, 118.7, 56.1, 44.4, 28.5, 15.2; HRMS (ESI-TOF) Calcd for C₁₁H₁₁ClN₄ [M+H]⁺: 235.0750; found 235.0758.

5-Azido-4-(4-fluoro-3-methoxyphenyl)pentanenitrile (3s). Prepared according to the general procedure B using alkene **1s** (48.3 mg, 0.32 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3s** (62.0 mg, 0.25 mmol, 79% yield) as a colorless oil. IR ν : 2973, 2903, 2248, 2100, 1611, 1517, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.07 (dd, J =10.8, 8.4 Hz, 1H), 6.81 (dd, J =8.0, 2.0 Hz, 1H), 6.77–6.71 (m, 1H), 3.91 (s, 3H), 3.55 (dd, J =12.4, 6.8 Hz, 1H), 3.47 (dd, J =12.4, 6.8 Hz, 1H), 3.01–2.89 (m, 1H), 2.34–2.25 (m, 1H), 2.23–2.05 (m, 2H), 1.95–1.81 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ : 151.9 (d, J =245 Hz), 148.1 (d, J =10.6 Hz), 135.6 (d, J =3.8 Hz), 119.5 (d, J =6.8 Hz), 118.9, 116.6 (d, J =18.3 Hz), 113.1 (d, J =2.0 Hz), 56.4, 56.4, 44.4, 28.7, 15.1; ¹⁹F NMR (376 MHz, CDCl₃) δ : -135.9; HRMS (ESI-TOF) Calcd for C₁₂H₁₃FN₄O [M+H]⁺: 249.1152; found 249.1154.

5-Azido-4-methyl-4-(1-tosyl-1H-indol-3-yl)pentanenitrile (3t). Prepared according to the general procedure B using alkene **1t** (97.4 mg, 0.31 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3t** (41.0 mg, 0.10 mmol, 32% yield) as a colorless oil. IR ν : 2925, 2248, 2103, 1370, 1173 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 8.02 (d, J =8.4 Hz, 1H), 7.74 (d, J =8.0 Hz, 2H), 7.59 (d, J =8.0 Hz, 1H), 7.39 (s, 1H), 7.34 (t, J =7.8 Hz, 1H), 7.29–7.20 (m, 3H), 3.64 (d, J =12.4 Hz, 1H), 3.58 (d, J =12.0 Hz, 1H), 2.43–2.30 (m, 4H), 2.14–1.98 (m, 2H), 1.89–1.92 (m, 1H), 1.48 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 145.2, 135.9, 134.8, 129.9, 128.1, 126.7, 125.0, 124.7, 123.6, 123.5, 120.6, 119.4, 114.4, 59.8, 40.0, 32.8, 22.6, 21.5, 12.5. HRMS (ESI-TOF) Calcd for C₂₁H₂₁N₅O₂S [M+H]⁺: 408.1489; found 408.1487.

4-(Azidomethyl)-4-methyl-6-phenylhexanenitrile (3u). Prepared according to the general procedure B using alkene **1u** (43.3 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3u** (47.0 mg, 0.18 mmol, 62% yield) as a colorless oil. IR ν : 2972, 2904, 2247, 2102, 1387, 1255, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.33–7.26 (m, 2H), 7.23–7.15 (m, 3H), 3.27 (d, J =12.4 Hz, 1H), 3.23 (d, J =12.4 Hz, 1H), 2.60–2.50 (m, 2H), 2.36–2.27 (m, 2H), 1.81–1.71 (m, 2H), 1.63–1.53 (m, 2H), 1.01 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 141.6, 128.5, 128.2, 126.1, 119.8, 59.1, 39.2, 37.3, 33.1, 29.9, 22.2, 12.0; HRMS (ESI-TOF) Calcd for C₁₄H₁₈N₄ [M+H]⁺: 243.1610; found 243.1611.

4-(Azidomethyl)-4-methylpentadecanenitrile (3v). Prepared according to the general procedure B using alkene **1v** (56.6 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3v** (39.5 mg, 0.14 mmol, 47% yield) as a colorless oil. IR ν : 2926, 2855, 2247, 2101, 1466, 1295 cm⁻¹; ¹H NMR

(400 MHz, CDCl₃) δ : 3.19 (d, J =12.4 Hz, 1H), 3.15 (d, J =12.4 Hz, 1H), 2.31–2.24 (m, 2H), 1.72–1.64 (m, 2H), 1.34–1.18 (m, 20H), 0.91 (s, 3H), 0.88 (t, J =6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ : 120.0, 59.4, 37.1, 36.9, 33.1, 31.9, 30.2, 29.59, 29.58, 29.56, 29.50, 29.3, 23.3, 22.7, 22.3, 14.1, 12.0. HRMS (ESI-TOF) Calcd for C₁₇H₃₂N₄ [M+H]⁺: 293.2700; found 293.2708.

2-Azido-5-cyano-3-phenylpentyl acetate (3w). Prepared according to the general procedure B using alkene **1w** (52.4 mg, 0.30 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3w** (29.7 mg, 0.11 mmol, 37% yield, 1.1/1 *dr*) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ : 7.41–7.30 (m, 3H), 7.26–7.22 (m, 0.58H), 7.20–7.14 (m, 1.52H), 4.22–4.17 (m, 0.28H), 4.05 (dd, J =11.6, 2.8 Hz, 0.72H), 3.95–3.82 (m, 1.32H), 3.82–3.73 (m, 0.84H), 3.00–2.90 (m, 0.29H), 2.8–2.69 (m, 0.68H), 2.49–2.36 (m, 0.70H), 2.32–2.17 (m, 1.2H), 2.09 (s, 0.89H), 2.07 (m, 2.02H), 2.06–1.88 (m, 2H); HRMS (ESI-TOF) Calcd for C₁₄H₁₆N₄O₂ [M+Na]⁺: 295.1171; found 295.1175.

5-Azido-4-methyl-4-phenylhexanenitrile (3x). Prepared according to the general procedure B using alkene **1x** (38.4 mg, 0.29 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3x** (29.6 mg, 0.13 mmol, 45% yield, 3.9/1 *dr*) as a colorless oil; ¹H NMR (400 MHz, CDCl₃) δ : 7.40–7.33 (m, 2H), 7.32–7.20 (m, 3H), 3.75 (q, J =6.8 Hz, 0.81H), 3.66 (q, J =6.4 Hz, 0.17H), 2.30–1.80 (m, 4H), 1.36 (s, 0.49H), 1.30 (s, 2.52H), 1.16 (d, J =6.8 Hz, 0.52H), 1.00 (d, J =6.8 Hz, 2.49H); HRMS (ESI-TOF) Calcd for C₁₃H₁₆N₄ [M+H]⁺: 229.1453; found 229.1462.

5-Azido-4-((8R,9S,13S,14S)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl)pentanenitrile (3y). Prepared according to the general procedure B using alkene **1y** (83.4 mg, 0.297 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3y** (44.3 mg, 0.12 mmol, 40% yield, *dr n.d.*) as a colorless oil. IR ν : 3668, 2973, 2905, 2100, 1736, 1051 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.27 (d, J =7.2 Hz, 1H), 6.96 (d, J =8.0 Hz, 1H), 6.92 (s, 1H), 3.55 (dd, J =12.4, 6.8 Hz, 1H), 3.46 (dd, J =12.4, 6.8 Hz, 1H), 2.91 (dd, J =8.4, 4.0 Hz, 2H), 2.51 (dd, J =19.2, 8.8 Hz, 1H), 2.46–2.37 (m, 1H), 2.35–2.22 (m, 2H), 2.22–2.00 (m, 5H), 2.00–1.85 (m, 2H), 1.71–1.56 (m, 3H), 1.56–1.40 (m, 3H), 0.92 (s, 3H), 0.89–0.82 (m, 1H); HRMS (ESI-TOF) Calcd for C₂₃H₂₈N₄O [M+H]⁺: 377.2336; found 377.2337.

2-(2-(Azidomethyl)-2-phenylcyclopentyl)acetone (5). Prepared according to the general procedure B using alkene **4** (59.0 mg, 0.30 mmol), TMSN₃ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **5** (44.8 mg, 0.19 mmol, 62% yield, *dr* 3.2/1) as a colorless oil. IR ν : 2958, 2098, 1498, 1460, 1262 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.42–7.21 (m, 5H), 3.65 (d, J =12.4 Hz, 1H), 3.57 (d, J =12.4 Hz, 0.84H), 3.41 (d, J =12.0 Hz, 0.21H), 2.71–2.55 (m, 1.70H), 2.52–2.42 (m, 0.22H), 2.42–2.30 (m, 0.86H), 2.25–2.10 (m, 2.32H), 2.09–1.97 (m, 1H), 1.93–1.63 (m, 3H); HRMS (ESI-TOF) Calcd for C₁₄H₁₆N₄ [M+H]⁺: 241.1448; found 241.1451.

Dimethyl 2-(2-azido-1-phenylethyl)succinate (3aa). Prepared according to the general procedure B using alkene **1p** (34.6 mg, 0.33 mmol), TMSN₃ (79 μ L, 0.6 mmol), diethyl fumarate (225 μ L, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3aa** (20.1 mg, 0.07 mmol, 21% yield, *dr* 2/1) as a colorless oil. IR ν : 2952, 2100, 1735, 1438 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ : 7.42–7.27 (m, 3H), 7.21–7.10 (m, 2H), 3.82–3.69 (m, 2.56H), 3.66 (s, 1.34H), 3.64–3.50 (m, 3.87H), 3.47–3.42 (m, 0.18H), 3.36–3.29 (m, 0.5H), 3.22–3.12 (m, 0.9H), 3.10–3.01 (m, 0.5H), 2.72 (dd, J =16.8, 9.6 Hz, 0.5H), 2.58 (dd, J =16.8, 10.8 Hz, 0.51H), 2.44 (dd, J =16.8, 4.8 Hz, 0.53H), 2.21 (dd, J =16.8, 3.6 Hz, 0.43H); ¹³C NMR (101 MHz, CDCl₃) δ : 172.0, 138.6, 138.1, 129.1, 128.7, 128.1, 127.9, 127.8, 54.7, 53.2, 52.2,

51.9, 51.8, 47.5, 47.0, 44.6, 44.3, 34.9, 33.6; HRMS (ESI-TOF) Calcd for $C_{14}H_{17}N_3O_4$ $[M+H]^+$: 292.1292; found 292.1287.

3-(2-Azido-1-phenylethyl)cyclohexanone (3ab). Prepared according to the general procedure B using alkene **1p** (31.3 mg, 0.3 mmol), $TMSN_3$ (79 μ L, 0.6 mmol), cyclohex-2-enone (173.0 mg, 1.8 mmol), MeOH (36 μ L, 0.9 mmol) and acetone (1.5 mL) as starting materials to afford **3ab** (22.7 mg, 0.21 mmol, 31% yield, 1/1 *dr*) as a colorless oil. IR ν : 2097, 1710, 1453, 1231 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.40–7.23 (m, 3.6 H), 7.20–7.10 (m, 1H), 7.10–6.92 (m, 0.4H), 3.96–3.67 (m, 0.80H), 3.67–3.57 (m, 1H), 3.50–3.23 (m, 0.24H), 3.02–2.90 (m, 0.31H), 2.82–2.60 (m, 0.74H), 2.59–2.49 (m, 0.41H), 2.48–2.29 (m, 1H), 2.27–2.12 (m, 1.36H), 2.12–1.86 (m, 2.62H), 1.85–1.46 (m, 3H), 1.46–1.31 (m, 0.49H), 1.30–1.14 (m, 0.62H). HRMS (ESI-TOF) Calcd for $C_{14}H_{17}N_3O$ $[M+H]^+$: 244.1444; found 244.1444.

4-Methyl-4-phenyl-5-(4-phenyl-1H-1,2,3-triazol-1-yl)pentanenitrile (6). To a overdried flask cooled under N_2 , **3a** (57.7 mg, 0.27 mmol), phenylacetylene (45 μ L, 0.41 mmol), CuI (78.9 mg, 0.41 mmol), DIPEA (135 μ L, 0.82 mmol) and MeCN (4 mL) were added. The resulting yellow mixture was stirred overnight at room temperature. The reaction mixture was condensed and the residue was passed through a pad of silica gel. The filtrate was condensed and purified by column chromatography (PE/EA=3/1) to give **6** (7.7 mg, 0.18 mmol, 68% yield) as a white solid (decomposed before melted). IR ν : 3061, 2978, 2248, 1464 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.63 (d, $J=7.2$ Hz, 2H), 7.45–7.32 (m, 5H), 7.31–7.20 (m, 3H), 6.85 (s, 1H), 4.60 (d, $J=13.6$ Hz, 1H), 4.47 (d, $J=13.6$ Hz, 1H), 2.46–2.33 (m, 1H), 2.26–2.13 (m, 1H), 2.13–1.99 (m, 2H), 1.39 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 147.2, 141.0, 130.4, 129.3, 128.8, 128.2, 127.9, 126.5, 125.6, 120.4, 119.4, 61.4, 42.7, 35.2, 21.2, 12.5. HRMS (ESI-TOF) Calcd for $C_{20}H_{20}N_4$ $[M+H]^+$: 317.1761; found 317.1776.

5-Amino-4-methyl-4-phenylpentanenitrile (7). To a solution of **3a** (64.0 mg, 0.30 mmol) in ethanol (3 mL), Pd/C (5 wt%, 8.3 mg) was added. The mixture was degassed through three freeze-pump-thaw cycles under H_2 . After stirred for 13 h at room temperature, the reaction mixture was filtered through silica gel and condensed *in vacuo* to obtain the product **7** (54.7 mg, 0.29 mmol, 97% yield) as a colorless oil. IR ν : 3385, 2973, 2903, 2102, 1387, 1072 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.36 (dd, $J=8.0, 7.2$ Hz, 2H), 7.31–7.20 (m, 3H), 2.95 (d, $J=13.2$ Hz, 1H), 2.74 (d, $J=13.2$ Hz, 1H), 2.23–2.08 (m, 2H), 2.07–1.84 (m, 2H), 1.35 (s, 3H), 0.91 (br s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 143.0, 128.8, 126.6, 126.4, 120.0, 53.6, 42.9, 35.8, 21.1, 12.5. HRMS (ESI-TOF) Calcd for $C_{12}H_{16}N_2$ $[M+H]^+$: 189.1386; found 189.1388.

Methyl 5-azido-4-methyl-4-phenylpentanoate (8).^[6] To a 25 mL round-bottom flask, **3a** (221.8 mg, 1.04 mmol) and methanol 1 mL were added, followed by 1 mL of HCl/1,4-dioxane (4 mol/L, 4 equiv.) at room temperature. After stirring for 24 h, 10 mL of the saturated sodium bicarbonate solution was added. The mixture was extracted with 10 mL ethyl acetate 5 times, and the organic phase was dried by sodium sulfate. The mixture was condensed and purified by column chromatography (PE/EA=11/1) to give **8** (169.3 mg, 0.68 mmol, 66% yield) as a colorless liquid, and **3a** was also obtained (54.7 mg, 25% recovery). IR ν : 2952, 2100, 1737, 1498, 1171 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.37–7.29 (m, 4H), 7.26–7.22 (m, 1H), 3.60 (s, 3H), 3.52 (d, $J=12.0$ Hz, 1H), 3.40 (d, $J=12.0$ Hz, 1H), 2.21–2.09 (m, 2H), 2.06–1.88 (m, 2H), 1.38 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 173.8, 143.1, 128.6, 126.7, 126.3, 62.8, 51.6, 42.1, 34.1, 29.1, 22.1; HRMS (ESI-TOF) Calcd for $C_{13}H_{17}N_3O_2$ $[M+H]^+$: 248.1394; found 248.1383.

5-Methyl-5-phenylpiperidin-2-one (9).^[14] To a solution of **8** (67.2 mg, 0.27 mmol) in methyl acetate (3 mL), Pd/C (5 wt%, 10 mol%, 57.4 mg) was added. The mixture was degassed through three freeze-pump-thaw cycles under H_2 . After being stirred for 24 h at room temperature, the reaction mixture was filtered through silica gel and condensed *in vacuo* to obtain the product **9** (28.5 mg,

0.15 mmol, 56% yield) as a colorless oil. IR ν : 3251, 2926, 1665, 1497 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.38–7.32 (m, 4H), 7.25–7.21 (m, 1H), 6.24–5.90 (br, 1H), 3.74–3.67 (m, 1H), 3.42–3.32 (m, 1H), 2.42–2.34 (m, 1H), 2.27–2.11 (m, 2H), 2.04–1.96 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 171.9, 144.6, 128.7, 126.6, 125.5, 51.9, 36.5, 33.3, 28.6, 27.3; HRMS (EI-TOF) Calcd for $C_{12}H_{15}NO$ $[M]^+$: 189.1154; found 189.1155.

4-Phenyl-2-(1-phenylvinyl)cyclopentanecarbonitrile (11). Prepared according to the general procedure A using alkene **10** (63.7 mg, 0.29 mmol), $TMSN_3$ (79 μ L, 0.6 mmol), acrylonitrile (120 μ L, 1.8 mmol), H_2O (54 μ L, 3 mmol) and MeCN (1.5 mL) as starting materials to afford **11** (72.7 mg, 0.26 mmol, 92% yield, major isomer/minor isomers 1.5/1) as a colorless oil. IR ν : 3029, 2237, 2102, 1494, 1451 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ : 7.45–7.22 (m, 10H), 5.45 (s, 1H), 5.29 (d, $J=1.2$ Hz, 1H), 3.47–3.37 (m, 1H), 3.37–3.25 (m, 1H), 3.11 (td, $J=8.4, 4.0$ Hz, 1H), 2.65 (dt, $J=14.0, 9.6$ Hz, 1H), 2.46–2.35 (m, 1H), 2.24–2.07 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ : 146.5, 143.6, 141.2, 128.7, 128.5, 127.8, 127.2, 126.7, 126.5, 121.2, 114.8, 47.7, 43.9, 38.7, 38.1, 33.8. HRMS (ESI-TOF) Calcd for $C_{20}H_{19}N$ $[M+H]^+$: 274.1590; found 274.1592.

Supporting Information

The supporting information for this article is available on the WWW under <https://doi.org/10.1002/cjoc.201800320>.

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Direct synthesis of dialkyl ketones from deoxygenative cross-coupling of carboxylic acids and alcohols†

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Carboxylic acids and alcohols are widely commercially available, structurally diverse, benchtop stable, and ubiquitous in both natural products and pharmaceutical agents, making them ideal coupling partners for organic synthesis. Though various transformations have been developed by enabling the activation and subsequent cross-coupling of carboxylic acids and alcohols in separate contexts, the direct coupling of these two structural motifs to build value-added molecules is rare. Herein, we developed a direct deoxygenative cross-coupling between carboxylic acids and alcohols for dialkyl ketone synthesis *via* photoredox/nickel dual catalysis. This protocol provides a powerful platform to construct a wide range of structurally diverse ketone scaffolds with broad substrate scope, good functional group tolerance, step-economy and mild reaction conditions, using simple and readily available substrates. Moreover, the large-scale synthesis and late-stage functionalization of biological molecules also demonstrate the potential practicality.

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Due to the prevalence of ketones in natural products and bioactive drugs¹ and their central role as versatile reactants in synthetic chemistry,² the development of powerful methods for ketone synthesis is highly desirable. In this context, a vast number of methods have been developed to construct ketones. Typically, ketone synthesis most often relies upon the addition of an organometallic reagent to an aldehyde followed by oxidation³ or more recently, the use of carboxylic acid derivatives to couple with various nucleophiles (Fig. 1a).⁴ While significant contributions have been made to this field, these methods typically necessitate a prefunctionalization step and often require nonabundant starting materials, such as air- and moisture-sensitive alkyl organometallics,^{4e,k-l} and organoboron and organosilicon reagents,^{4c-e} which are not step-economical and might lead to issues with functional group tolerance and waste generation, thereby limiting the reaction scope and practicality. To address this problem, we sought to develop a robust platform to deliver ketones utilizing easily accessible and commercially available starting materials under mild conditions.

Carboxylic acids and alcohols are widely commercially available, structurally diverse, benchtop stable, relatively

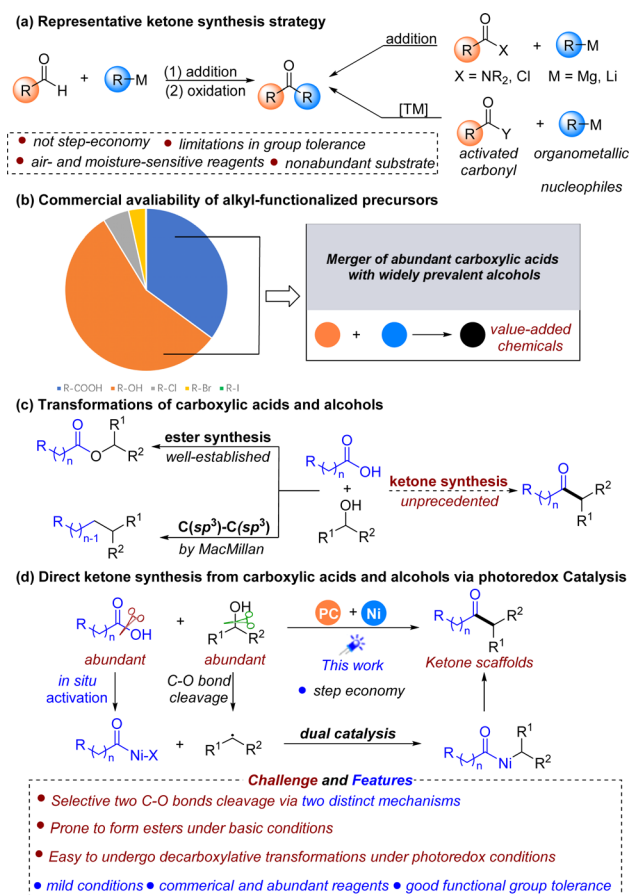


Fig. 1 Background of ketone synthesis and cross-coupling of carboxylic acids and alcohols.

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nontoxic, and ubiquitous in both natural products and pharmaceutical agents,⁵ making them ideal coupling partners for organic synthesis (Fig. 1b). In recent years, a variety of transformations have been developed by enabling the activation and subsequent cross-coupling of carboxylic acids and alcohols *via* metallaphotoredox catalysis in separate contexts.⁶ The direct coupling of these two prevalent structural motifs to build value-added molecules is significantly rare but highly of interest. Conventionally, alcohols and carboxylic acids are most commonly coupled to form esters,⁷ and fragment cross-coupling of these two structural motifs has been explored to a lesser extent. Recently, the efficient direct coupling of carboxylic acids and alcohols to forge new C(sp³)-C(sp³) bonds has been developed *via* an N-heterocyclic carbene (NHC)-promoted deoxygenation process by the MacMillan group (Fig. 1c, left).⁸ Despite this great achievement, developing new types of cross-coupling reactions between these two molecules has remained an appealing yet elusive goal. Considering the importance of ketone scaffolds, we wondered if diverse ketones could be accessed from the direct coupling of abundant carboxylic acids and alcohols, where acids serve as acyl electrophiles, and alcohols serve as nucleophiles (Fig. 1c, right). On this subject, Hong developed a photoinduced method for synthesizing ketones from alcohols and carboxylic acid derivatives through NHC catalysis under mild reaction conditions.^{6g} This approach worked well for benzoic acid, but was not effective for the alkanolic acid substrates. As a consequence, developing an efficient and new catalytic methodology to convert carboxylic acids and alcohols into dialkyl ketone scaffolds is still highly of interest and would complement Hong's strategy.

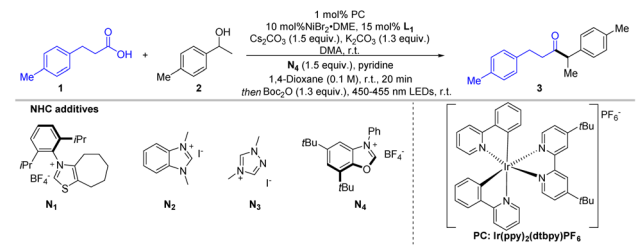
However, direct coupling of these two structural motifs forming ketones in a desired manner is not as easy as might be expected due to the potential competing cleavage of two C-O bonds in these two molecules. The main challenge for realizing this transformation was how to selectively achieve C-O bond cleavage in both alcohols and carboxylic acids *via* two distinct mechanisms. In recent years, the combination of photoredox and nickel catalysis has emerged as a powerful tool in chemical bond construction,⁹ which might provide an alternative protocol for the ketone preparations from alcohols^{10,11} and acids. In such a reaction, a transition-metal catalytic unit could engage sequentially with the acyl electrophiles formed *in situ* from carboxylic acids¹² and radicals generated from alcohols through oxidative addition¹³ and radical capture.^{12a,14} Then the resulting diorganonickel adduct undergoes reductive elimination to afford the desired ketone scaffolds (Fig. 1d). Nevertheless, to achieve this goal, other potential competing reactions, such as the esterification reaction^{6f} and decarboxylative transformation,^{15,6e,h,i} which are commonly encountered under basic and photoredox conditions, are also a big problem and need to be avoided.

In this work, we developed a photoredox-catalyzed synthetic protocol for diverse dialkyl ketone synthesis from naturally abundant carboxylic acids and alcohols under mild conditions with good functional group compatibility, and broad substrate scope. This protocol features no protection and deprotection steps. Given the structural diversity of carboxylic acids and

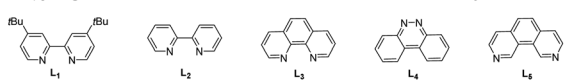
alcohols, the success of this protocol could potentially enhance the synthesis of complex ketones. More significantly, ketones can be directly constructed from two abundant starting materials, thus expanding the existing ketone synthetic routes.

To start our investigation, the synthetic method for ketones was explored with the commercially available carboxylic acid **1** and alcohol **2** as the model substrate (Table 1). Based on previously reported elegant carboxylic acid activations in ketone synthesis,^{6h,j,12a,14} Boc₂O was chosen as the activating reagent to generate mixed anhydride *in situ* from carboxylic acids. After extensive reaction condition screening (see the ESI† for details), we were pleased to find that the corresponding ketone **3** was obtained in 73% isolated yield using **N4** as the alcohol-activating agent and Cs₂CO₃/K₂CO₃ and pyridine as bases in the presence of a catalytic amount of NiBr₂·DME and **L1** under visible light irradiation in DMA/1,4-dioxane using Ir(ppy)₂-(dtbbpy)PF₆ as the photocatalyst (entry 1). The thiazole-based NHC reagent **N1** and other simple triazole-based NHC molecules **N2** and **N3** are ineffective in this transformation (entry 2). These initial optimization studies revealed the importance of NHC types for the reaction efficiency. A slightly lower yield was obtained when *t*BuOMe was used instead of 1,4-dioxane (entry 3). Other solvents, such as benzotrifluoride, tetrahydrofuran and acetonitrile were also tested and the results indicated that

Table 1 Optimization of reaction conditions^a



Entry	Variation from optimized conditions	Yield ^b (%)
1	None	75 (73)
2	N1 , N2 , and N3 instead of N4	0, trace, 0
3	BuOMe instead of 1,4-dioxane	60
4	PhCF, THF, and MeCN instead of 1,4-dioxane	54, 13, <10
5	L2 , L3 , L4 , and L5 instead of L1	37, 32, 30, trace
6	5 mol% NiBr ₂ ·DME, 7.5 mol% L1	78 (75)
7	No light irradiation	0
8	No NHC	0
9	No PC	0



^a Reaction conditions: **1** (0.3 mmol), **2** (0.42 mmol), 1 mol% Ir(ppy)₂-(dtbbpy)PF₆, 10 mol% NiBr₂·DME, 15 mol% **L1**, Cs₂CO₃ (0.45 mmol), K₂CO₃ (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc₂O (1.3 equiv.), 450–455 nm LEDs.

^b Yields of **3** were determined by ¹H NMR spectroscopy with mesitylene as an internal standard and the isolated yield is shown in parentheses. r.t., room temperature; NHC, N-heterocyclic carbene; DME, 1,2-dimethoxyethane; DMA, *N,N*-dimethylacetamide.



1,4-dioxane was more suitable for this transformation (entry 4). Screening of a range of ligands revealed that acylation product **3** could also be generated, albeit in diminished yields (entry 5). A slight increase in the yield was observed on reducing the amount of $\text{NiBr}_2 \cdot \text{DME}$ and **L1** (entry 6). Light irradiation was essential for this transformation as it did not progress under dark conditions (entry 7). Further control experiments showed that NHC and the photocatalyst were indispensable in this transformation (entries 8–9). It was worth noting that the side products due to decarboxylation and esterification could be detected.

With the optimized reaction conditions in hand, we then investigated the scope of carboxylic acids and alcohols (Fig. 2). We first probed the ability of various aliphatic acids for cross-coupling in our system (3–22). Substituted phenyl propionic acid and butyric acid derivatives yielded desired products in moderate to good yields (3–10). A range of aliphatic acids, including linear and cyclic acids, were amenable substrates, providing the cross-coupling products in good to excellent yields (11–18). Notably, carboxylic acids with additional functionalities were also compatible with this protocol. For example, various functional groups, such as alkyl chloride, ester, protected amine and ketone remain intact to furnish the

corresponding cross-coupling products, potentially allowing for the subsequent orthogonal functionalization (15–19). In particular, carboxylic acids with synthetic handles, such as halide (**10** and **15**), were readily incorporated into the accessible ketone scaffolds, which highlights the potential applications for the incorporation of these scaffolds into more complex targets. Products derived from alkenyl acids were also tolerated, as demonstrated by β,β -dimethylacrylic acid (**20**) and lineoic acid (**21**). These results show the great potential for structural modification and resource utilization of naturally existing carboxylic acids. Heterocycle-containing carboxylic acid reacted smoothly in this system, affording the deoxygenated cross-coupling product in moderate yield (**22**). Of particular note is that substituted phenyl acetic acid and hindered carboxylic acids (**23**), such as *N*-Boc proline (**24**) and 2-phenyl propionic acid (**25**) were not suitable for this transformation, yielding no product. Additionally, experiments with various benzoic acid derivatives were also performed under the standard conditions. Unfortunately, these substrates were not compatible with our system (**26–27**). This phenomenon could be attributed to the diminished reactivity in carboxylic acid activation.

Having established that this transformation tolerates various carboxylic acids, we turned our attention towards evaluating the scope of alcohol components. Consistent with our expectation, we were pleased to find that a wide variety of primary alcohols were successfully applied in this protocol, furnishing the desired ketones in moderate yields (28–32). The instability of the corresponding alkyl radicals originating from alcohols could be responsible for the relatively lower yield (29–32). Of particular note is that the developed protocol was also tolerant of the alcohol containing protected amine, as demonstrated by **31**, which was isolated in 40% yield. Notably, the alkene-retained product (**32**) was obtained in 39% yield, while intramolecular radical cyclization was not observed. This result suggests the faster capture of the alkyl radical than 5-*endo*-trig cyclizations under the specific reaction conditions. Secondary alcohols, especially cyclic alcohols, ranging from four- to seven-membered rings, were found to be viable coupling partners, successfully delivering the corresponding products in 40–61% yields (33–38). It is noteworthy that sterically encumbered polycyclic alcohols, such as 2-adamantanol, were employed without an appreciable decrease in the reaction efficiency (37). A relatively increased yield was obtained when benzyl alcohols were used, which is in line with the stability of the corresponding radical intermediates from alcohols (38–41). With these positive results in hand, we finally tested the feasibility of tertiary alcohols, such as 1-methylcyclohexanol and *tert*-butanol, and the experimental results indicated that no corresponding cross-coupling product could be observed (42–43).

Given the exceptionally mild and simple conditions, we sought to demonstrate the utility of this operationally convenient method in the late-stage functionalization of complex molecules. As shown in Fig. 3, the oxaprozin analogue **44** could be generated efficiently with our strategy in 55% yield. Lithocholic acid analogues could also undergo smoothly, providing the deoxygenative ketone in 60% and 62% yield, respectively (45 and 46). With stearic acid as an acyl donor, the

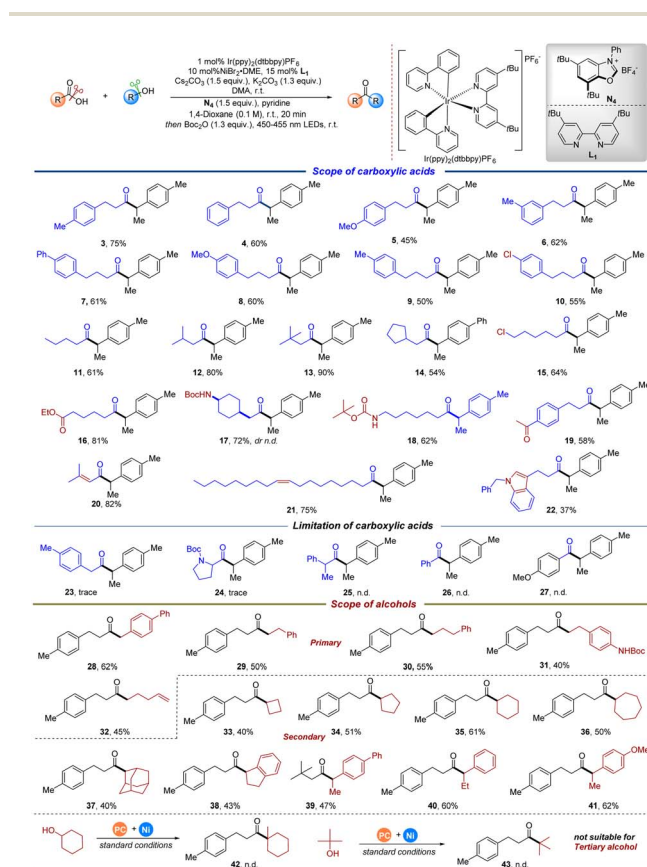


Fig. 2 Substrate scope for ketone synthesis. Standard conditions: carboxylic acid (0.3 mmol), alcohol (0.42 mmol), 1 mol% $\text{Ir}(\text{ppy})_2(\text{-dtbbpy})\text{PF}_6$, 10 mol% $\text{NiBr}_2 \cdot \text{DME}$, 15 mol% **L1**, Cs_2CO_3 (0.45 mmol), K_2CO_3 (1.3 equiv.), DMA (3 mL), **N4** (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc_2O (1.3 equiv.), 450–455 nm LEDs. Isolated yield.



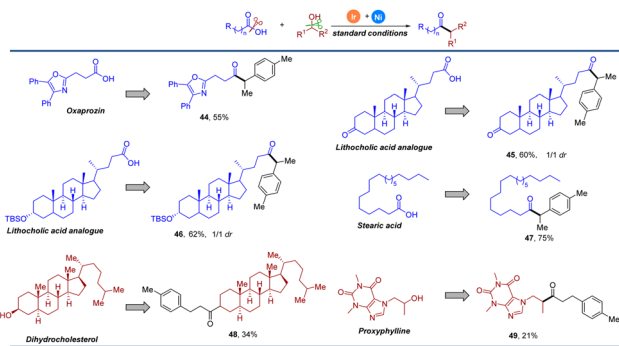


Fig. 3 Late-stage functionalization. Standard conditions: carboxylic acid (0.3 mmol), alcohol (0.42 mmol), 1 mol% Ir(ppy)₂(dtbbpy)PF₆, 10 mol% NiBr₂·DME, 15 mol% L₁, Cs₂CO₃ (0.45 mmol), K₂CO₃ (1.3 equiv.), DMA (3 mL), N₄ (1.5 mmol), pyridine (1.4 equiv.), 1,4-dioxane (3 mL), Boc₂O (1.3 equiv.), 450–455 nm LEDs. Isolated yield.

transformation proceeded efficiently, yielding **47** in 75% yield. A naturally occurring steroid was also successfully employed and afforded the corresponding product **48** in moderate yield. Bronchodilator proxyphylline showed good reactivity to deliver the product **49** in 21% yield. These results show great potential for the structural modification of an array of complex biological molecules, especially in medicinal chemistry.

To further showcase the synthetic utility of this developed strategy, a large-scale experiment was conducted, providing the desired ketone **3** in 71% yield (Fig. 4). There was almost no change in the chemical yield, suggesting that large-scale chemical production might be possible.

To gain further insight into the reaction mechanism, a series of mechanistic studies were performed (Fig. 5). In the presence of radical trap TEMPO, the reaction was completely shut down (Fig. 5a), indicating that a radical intermediate might be involved in this transformation. More importantly, a benzyl-trapped product, 2,2,6,6-tetramethylpiperidin-1-yl benzoate **50** was observed *via* high resolution mass spectrometry, further supporting that the reaction proceeds through a radical deoxygenative pathway and the intermediacy of a benzylic radical. Furthermore, the generation of a benzylic radical from **2** in the reaction also could be demonstrated by the observation of **51** when phenyl vinyl sulfone was added to the system. Additionally, to further elucidate the possible reaction pathway, a radical clock experiment was performed with cyclopropanemethanol **52** and the observation of ring-opening product **53** suggested the involvement of a radical intermediate (Fig. 5b). In our hypothesis, carboxylic acid is activated by Boc₂O, leading to the corresponding acyl-Ni oxidative insertion complex. The control experiments are consistent with this hypothesis. First, when

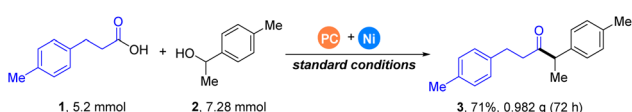


Fig. 4 Large-scale synthesis.

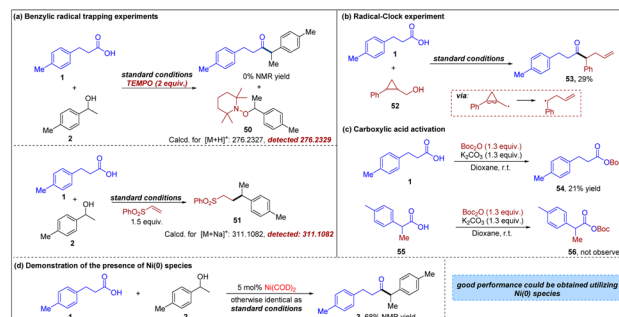


Fig. 5 Mechanistic studies.

primary carboxylic acid **1** is treated with Boc₂O and K₂CO₃, moderate conversion to the expected mixed anhydride is observed within 3 h (Fig. 5c). In the parallel experiment using secondary carboxylic acid **55**, there is no observable formation of the mixed anhydride **56** at the same time point, resulting in the formation of the acyl-Ni complex being difficult. These results are in line with the limitations of carboxylic acids shown in Fig. 2. It is noteworthy that the desired ketone **3** could be detected in 68% NMR yield when Ni(COD)₂ was used in place of NiBr₂·DME (Fig. 5d), indicating the presence of Ni(0) species.

Based on the previously reported literature^{6d,f,16} and the aforementioned mechanistic studies, a plausible mechanism for this transformation is proposed in Fig. 6. The proposed mechanism starts with the condensation of alcohol and NHC (N₄), providing activated alcohol **57**. Upon irradiation with visible light, the photocatalyst Ir(ppy)₂(dtbbpy)PF₆ **I** is known to access the highly oxidizing excited state species **II** (*Ir^{III}) ($E_{1/2}^{red}(*Ir^{III}/Ir^{II}) = +0.66$ V vs. SCE),¹⁷ which could be reductively quenched by the activated alcohol **57**, affording aminium radical cation **58**. Then a deprotonation process occurred at the α -position of **58**, yielding radical intermediate **59**. Subsequent β -scission occurred, thus generating the key alkyl intermediate **60**. The nickel catalytic cycle is initiated by the oxidative addition of the Ni(0) catalyst **62** to an *in situ*-activated carboxylic acid **61** formed by Boc₂O under basic conditions, to afford Ni(II) species **64**. Subsequently, efficient trapping of the alkyl radical

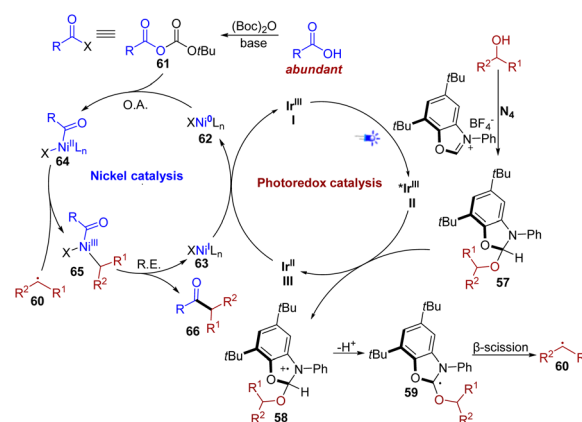


Fig. 6 A plausible mechanism.

60 provides Ni(III) complex **65**, which undergoes reductive elimination to yield the desired ketone **66** and Ni(I) complex **63**. Finally, the single electron transfer between Ni(I) species **63** and reduced photocatalyst **III** (Ir^{II}) regenerates the ground-state photocatalyst **I** (Ir^{III}) and the Ni(0) catalyst, completing both catalytic cycles.

Conclusions

In summary, we have developed a direct deoxygenative cross-coupling between carboxylic acids and alcohols for ketone synthesis *via* photoredox/nickel dual catalysis under mild conditions. This protocol provides a powerful platform to construct a wide range of structurally diverse ketone scaffolds with broad substrate scope, good functional group tolerance, step-economy and mild reaction conditions, using simple and readily available carboxylic acids and widely abundant alcohols as starting materials. Given the structural diversity of carboxylic acids and alcohols, the success of this metal-photoredox-catalyzed deoxygenative cross-coupling protocol could potentially enhance the synthesis of complex ketones. In addition, this developed method will promote the resource utilization of naturally abundant acids and alcohols and enhance the preparation of ketone scaffolds. The exact roles of carboxylic acids and alcohols were demonstrated by mechanistic studies, as we hypothesized, that the carboxylic acids provide the acyl group and the alcohols afford the alkyl group. Asymmetric transformations of carboxylic acids and alcohols into ketones are underway in our laboratory and will be reported in due course.

Data availability

The ESI[†] is available and includes experimental procedures for all reactions and characterization data for all products, including ¹H and ¹³C spectra and HRMS data.

Author contributions

Conceptualization and funding acquisition were done or provided by B. Y.; resources and supervision were done by B. Y.; project administration, data curation, investigation and formal analysis were done by B. Y. and R.-Y. T.; writing was done by B. Y. and revised by B. Y. and R.-Y. T.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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证书号第 3509466 号



发明专利证书

发明名称：一种 β -叠氮醇类化合物的制备方法

发明人：陆展;杨波

专利号：ZL 2017 1 0298525.1

专利申请日：2017 年 04 月 28 日

专利权人：浙江大学

地址：310058 浙江省杭州市西湖区余杭塘路 866 号

授权公告日：2019 年 08 月 30 日

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第 1 页 (共 2 页)

其他事项参见背面

证书号第6745770号



发明专利证书

发明名称：一种1,4-二羰基化合物的制备方法

发明人：祝诗发;杨波;王永东;黄志鹏

专利号：ZL 2021 1 0593153.1

专利申请日：2021年05月28日

专利权人：广州自远生物科技有限公司
心远（广州）药物研究有限公司;华南理工大学
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发明人：

祝诗发;杨波;王永东;黄志鹏



華南農業大學
South China Agricultural University

大学生创新创业训练计划 项目申报书模板

项目名称	调控水稻抗逆生长的有机硒功能试剂研究
项目类型	<input checked="" type="checkbox"/> 创新训练项目 <input type="checkbox"/> 创业训练项目 <input type="checkbox"/> 创业实践项目
所在学院	材料与能源学院
项目负责人	钟锦荣
项目负责人学号	202233510131
指导教师	汤日元，杨波
起止年月	2024年5月—2025年8月

华南农业大学创新创业学院 制

二〇二三年三月

一、基本情况

项目名称	调控水稻抗逆生长的有机硒功能试剂研究						
所属学科	能源化工（包括化学、材料科学、能源科学与技术、化学工程、纺织科学技术、食品科学技术、环境科学技术、安全科学技术等）						
项目来源	<input type="checkbox"/> A、学生自主选题，来源于自己对课题的长期积累与兴趣 <input checked="" type="checkbox"/> B、学生来源于教师科研项目选题 <input type="checkbox"/> C、学生承担社会、企业委托项目选题 <input type="checkbox"/> D、拔尖专项 <input type="checkbox"/> E、竞赛专项 <input type="checkbox"/> F、研修专项						
申请金额	1万元	项目期限	1.5年	拟申报项目级别		国家级	
负责人	钟锦荣	性别	男	民族	汉族	出生年月	2003年12月
学号	202233510131	联系电话	13431882262				
指导教师	汤日元，杨波	联系电话	13825112030				
项目简介	<p>为响应国家粮食安全战略，提高水稻的生产效率与质量，本课题拟开发稳定、安全的有机硒功能试剂，诱导激活水稻的抗盐碱能力。研究内容包括:(1)有机硒功能试剂及其剂型的研发;(2)有机硒功能试剂活性的初步筛选;(3)有机硒功能试剂对水稻种子萌发及幼苗生长发育调控效应;(4)有机硒功能试剂对水稻盐胁迫缓解效应的研究。项目研究将为水稻盐碱、海水等环境中的种植，以及提高机械播种发芽率，提供技术支持。</p>						
负责人曾经参与科研的情况	<p>自2023年5月加入了导师科研室，参加了“有机硒功能试剂”的项目研究，掌握了有机硒的制备、分离、提纯技术，以及水稻的种植技术。</p>						
指导教师承担科研课题情况	<p>近3年承担项目1A、1B、1C，横向项目2项。</p>						
指导教师对本项目的支持情况	<p>提供5万元以上的经费支持、为每个项目成员提供实验台位、提供所需的试剂耗材、提供全程指导。</p>						

项目组主要成员	姓名	学号	学院	专业 班级	联系电话	项目分工
	钟锦荣	202233510131	材料与能源学院	22 级 应 用 化 学 创新1 班	13431882262	负责统筹规划项目的计划安排和人员分工
	张欣欣	202133510326	材料与能源学院	21 级 应 用 化学3 班	13437870420	有机硒功能试剂的合成
	杜宇默	202233510206	材料与能源学院	22 级 应 用 化 学 创新1 班	18703708616	有机硒功能试剂的合成
	胡汶琪	202213110210	材料与能源学院	22 级 制 药 21 班	13042045773	有机硒试剂对水稻暴露于盐碱环境下的调控研究
	杨蕾	202333510225	材料与能源学院	23 应 用 化 学2班	15970137081	有机硒试剂对水稻暴露于盐碱环境下的调控研究
	杨波		材料与能源学院		18818914392	
指导教师	汤日元		材料与能源学院		13825112030	
	杨波		材料与能源学院		18818914392	

二、 立项依据

1 研究目的

开发具有优良光热稳定性、水溶性、生物兼容性、内吸输导性、安全的有机硒功能试剂，具有调控水稻抗干旱、抗盐碱的功能，提高水稻的抗逆能力，为水稻在相对干旱区域和盐碱地带种植提供技术支持，对国家粮食安全战略有重大意义。

2 研究内容

我们开展以下三个方面的工作：

2.1 有机硒功能试剂及其剂型的研发；

探讨基于类碱基和氨基酸类化合物与无毒单质硒的耦合技术，探究有机硒与植物必需矿物质元素耦合的稳定化技术（图 1），制备出绿色、安全、稳定，适用于水培和土培种植的有机硒试剂配方。

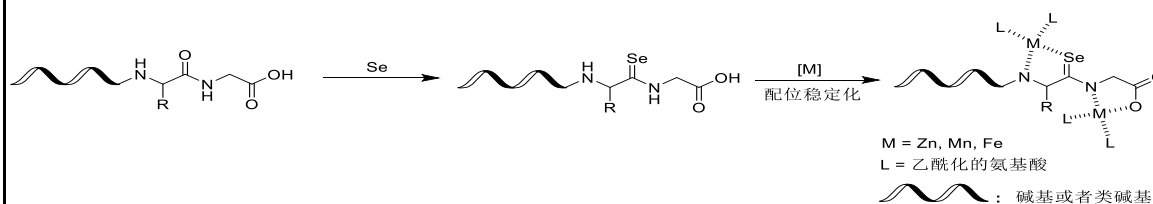


图1 有机硒的稳定性

2.2 有机硒功能试剂对水稻种子萌发及幼苗生长发育调控效应；

以水稻为研究对象，通过纸上催芽法等实验方法，探究有机硒功能试剂对种子萌发及内源激素的调控效应，同时对其毒理性进行评估，筛选出最具植物生长调节活性、环境友好型有机硒功能试剂。

结合水培、滴灌、叶面喷施等技术手段，调控有机硒功能试剂在水稻中的生物转化，通过分析有机硒在水稻体内代谢、转运途径，从表型及分子水平验证有机硒转运相关基因的功能，从农药与植物互作的角度提出控制有机硒功能试剂的定向积累和靶向释放的新策略，为高品质农产品的标准化种植提供数据支撑。

2.3 有机硒功能试剂对水稻盐胁迫缓解效应的研究；

通过考察有机硒功能试剂对盐胁迫条件下水稻生长发育的影响，并分别从形态、生理生化、基因的转录水平方面开展具体的研究，探究水稻体内有机硒功能试剂— (GSH-PX)

合成及代谢途径，拟为有机硒功能试剂进一步拓展应用范围，为解决目前水稻盐害及未来海水稻的栽培育种方式提供了有效的科学考究。

3 国内外研究现状和发展动态

3.1 有机硒在生物领域的研究进展

硒的生物学功能主要是通过与硒结合形成硒蛋白实现的，其具有多样的生物学功能：能够促进动物生长，提高繁殖机能；增强机体的抗氧化能力，改善动物的免疫功能^[1]。在研究硒生物作用的初期，人们关注的重点是硒的毒理作用。直到1973年谷胱甘肽过氧化酶的发现，硒的生物化学研究才真正开始。谷胱甘肽过氧化酶与人类肿瘤、糖尿病、心血管疾病及神经退行性疾病的种种关系，使得人们更加了解和重视硒与人类和动物健康的联系。继谷胱甘肽过氧化酶之后，人们还从哺乳动物中发现硒为多种酶所必需，如：碘甲腺原氨酸脱碘酶、磷脂过氧化氢谷胱甘肽过氧化物酶、硫氧还蛋白还原酶等^[2]。这些酶的抗氧化能力极强，能清除有害的自由基，阻断自由基的反应，从而减少环境中有害物质对机体器官的侵害，维持机体的正常免疫功能、生育功能等，对机体进行全面的保护^[3]。

3.2 缓解重金属的毒害、提高抗病能力

马洁等^[4]研究表明，于分蘖期叶面喷洒生物有机硒肥（一株十分耐硒、且能分泌水溶性有机硒的菌株），喷施有机硒后，受品种响应程度的影响，大多数的水稻茎砷、镉含量均有不同程度的下降，降低对水稻叶和稻米对镉的富集。这表明了硒可以缓解重金属对水稻的毒害。柳迎杰等^[5]研究表明，喷施有机硒肥（生物纳米有机硒肥、螯合硒肥、绿维康有机硒肥）能增加马铃薯产量和块茎硒含量，显著提高平均单薯重，并提高块茎中营养物质的含量，如干物质、淀粉、还原糖、VC等，显著提高抗氧化酶活性。这说明一定量的有机硒肥能够促进马铃薯的物质积累，提高抗病能力。

3.3 促进种子的生长

王淑英等^[6]研究表明，有机硒液体肥（硒含量>200 mg/kg，有效活菌数≥2亿CFU/mL）浸泡玉米种子，结果发现硒肥引发玉米种子经过低温逆境，能显著增加玉米幼苗和根系的生长。加快了玉米种子发芽期根系和茎叶的生长。经有机硒液体肥引发处理的玉米种子在低温吸胀后发芽，种子活力指数显著提高。主根生长长度的活力指数明显高于茎叶生长长度的活力指数，但茎叶重量的活力指数显著高于根系重量的活力指数，即有机硒肥处理玉

米种子具有显著的促根壮苗作用。

3.4 有机硒对植物盐胁迫下的抗逆性研究进展

土壤盐渍化是一种全球性的环境挑战，限制了全球8亿公顷的作物产量。由于 Na^+ 的积累，遭受高盐胁迫的植物经常表现出 Na^+ 毒性的症状，这反过来又减少了养分的获取，导致营养失衡和氧化损伤^[7]。在高盐度土壤中，植株因高渗透压的影响出现渗透胁迫，致使叶绿体超微结构损伤，呼吸气孔受限甚至关闭，使光合、呼吸作用的速率降低^[8]。高盐度产生的离子毒性会破坏细胞质膜结构，阻碍植物对有益生长的矿质元素的吸收。此外，盐胁迫还会引发次生胁迫效应，如氧化应激通常伴有干旱胁迫等^[9]。

在盐胁迫下，施加有机硒的主要作用为清除活性氧、提高植株抗氧化性，减轻盐胁迫造成的伤害。其次，硒作为超氧化物歧化酶(SOD)、过氧化物酶(POD)、过氧化氢酶(CAT)等抗氧化酶的辅酶因子，其浓度的增加进而对抗氧化酶的活性进行提升，增强植株抗氧化活性，显著降低了植物体内的ROS浓度和丙二醛(MDA)含量^[10]。大量实验表明硒在保护植物免受盐诱导的胁迫中起积极作用^[11]。Shimaa A.^[12]研究表明，用纳米硒浸种和生长发育关键期叶面喷施，能够改善盐胁迫下根系发育、激活抗氧化系统、提高根系生物量。YaSin等^[13]研究表明，通过用亚硒酸钠浸种，能够提高盐胁迫下芸苔属植物的种子萌发率和叶绿素含量。对于盐胁迫下的小麦，Yigit等^[14]研究发现，外源硒的加入明显抑制了盐胁迫下细胞质膜透性的升高，可以有效缓解盐胁迫对植株造成的损害。近期也有研究发现，随着盐胁迫下外源硒的施加，小麦对氮、钾、钙的摄取有明显提高，引发植物体内更多氨基酸、代谢产物以及应激信号的产生^[15]。

3.5 应用前景

本项目预期研制出一种调节水稻抗干旱和抗盐胁迫的类植物激素有机硒试剂，其应用前景如下：

(1) 为了践行国家粮食安全战略，把饭碗牢牢端在自己手中，水稻种植地由水田拓展到相对干旱的山地、盐碱地带、以及临海滩涂地。水稻要正常生产必须解决干旱和盐碱胁迫的现实问题。有机硒功能试剂能显著提高水稻的抗逆能力，为水稻的正常生长和高产提高技术支持。

(2) 随着现代农业机械的发展，机械直接播种技术得到了发展，但是需要提高水稻种

子的发芽率和抗逆能力, 本项目开发的有机硒功能试剂能有效提高种子发芽率和抗干旱、抗盐胁迫能力, 确保种子在田间的正常生长。因此有机硒功能试剂可以作为机械直接播种前种子处理剂。

(3) 有机硒功能试剂具有很好的生物兼容性和内吸输导性, 可以有效被水稻吸收生物转化成功能有机硒, 生产高附加值的富硒大米, 对农业高质量发展有重要价值。

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4 创新点与项目特色

本项目研制的类激素唑硒酮功能试剂的化合物结构、制备技术、用途均有自主知识产权，属于原创的功能活性分子。目前，用于农作物生长调节的主要有高毒的亚硒酸盐，难制备的纳米硒耦合试剂，以及高成本的酵母硒试剂，未见有基于植物激素结构设计开发的有基硒功能试剂。本项目开发的唑硒酮功能试剂具有优良的抗氧化性、生物兼容性、内吸传导性、高剂量安全性、水溶性，以及稳定性，易制备、有规模化应用的优势。

5 技术路线、拟解决的问题及预期成果

5.1 技术路线

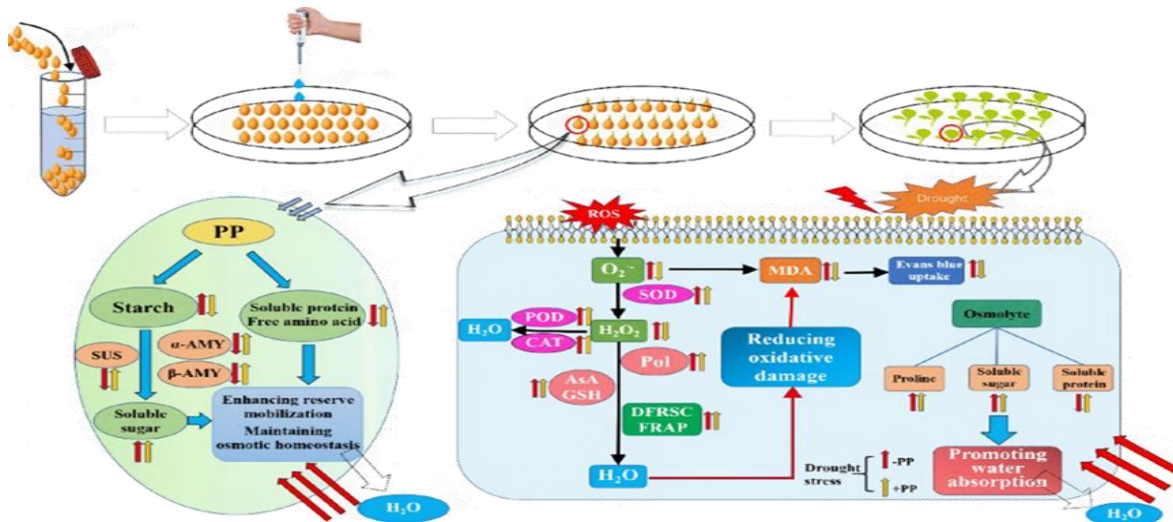


图 3 有机硒试剂调控水稻种子和苗期的抗逆性思维图

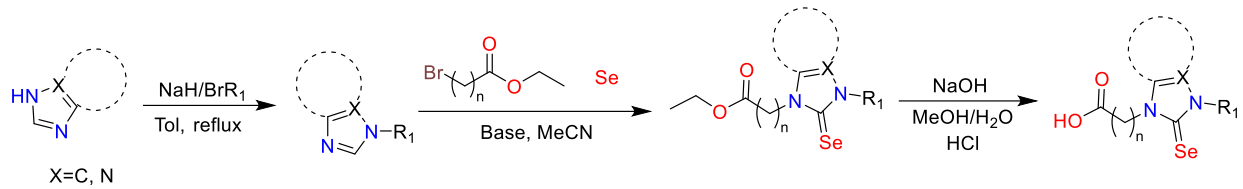


图 4 有机硒功能试剂的合成路线

5.2 有机硒功能试剂活性的初步筛选

为了获取高效、低毒、环境友好的有机硒功能试剂，我们针对上一章所合成有机硒类衍生物作为筛选对象，首先通过自由基离子清除实验筛选，再通过水稻发芽试验，考察化合物对发芽率，发芽势，发芽指数的影响，并考察优选化合物对种子根中内源激素含量的影响。

5.2.1 自由基清除实验

通过测定化合物的DPPH脱色能力，可以准确地评估它们的抗氧化性能。随着517 nm处的吸光度显著下降，自由基从原本的紫色变成了浅色，这表明了该物质具有良好的自由基清除能力。

具体实验步骤是：将20 ml不同浓度的测试样品与180毫升或 DPPH 溶液在黑暗中混合30分钟。然后，在微板读取器上测量DPPH在517 nm处的吸光度变化。抗坏血酸被用作阳性对照，而DMSO则被用作阴性对照。

抗氧化活性计算如下：抗氧化活性=[(对照吸光度-样品吸光度)/对照吸光度]*100%。

5.2.2 有机硒化合物活性筛选

将有机硒化合物分别配制成 0 mg/L、0.5 mg/L、1.0 mg/L、2.0 mg/L、5.0 mg/L和 10 mg/L 浓度梯度。试验以清水为阴性对照，以DA-6为阳性对照（浓度为10.0 mg/L，参照药品实际施用量）。

通过纸上催芽法进行种子发芽实验。挑选大小一致、成熟饱满的水稻种子并用3%的次氯酸钠水溶液除菌5 min，然后用去离子水或者双重蒸馏水漂洗种子10 min(整个过程中需要3-5次换水)，漂洗完成后立即用滤纸吸干种子表面的水分备用。25 °C下用以上准备好的各浓度药液浸泡水稻种子8 h，药剂与种子体积比例范围为2.5:1(v/v)；然后沥水并用滤纸吸取种子表面多余的水分，将种子播种于培养钵中，每个培养钵摆放20粒，每钵为一个处理，每个处理4次重复。播种完成后用保鲜膜封口并用牙签扎5个小孔，随后25°C±2 °C培

养箱中黑暗培养，培养48h后测定水稻发芽情况。

5.2.3 目标化合物对水稻种子根生长发育影响的评估

当A%和B%值在0-30%时，表示所测化合物在该浓度条件下具有重度抑制根系生长的效应，可用于除草剂研究；当值变化范围在30%-90%之间，表示所测试化合物在该浓度下具有中轻度抑制根系发育的效应，可用于植物生长调节剂的研究；当值变化范围91%-110%时，所测试化合物在该浓度下可以被判定对根生长发育影响忽略不计；当值变化范围大于110%时，则可判定该化合物在此浓度下具有促进根系发育的活性，可作物植物生长促进剂研究。

$$\text{主根伸长率(A\%)} = \frac{\text{处理主根长度}}{\text{对照主根长度}} \times 100\%$$

$$\text{侧根促进率(B\%)} = \frac{\text{处理侧根数量}}{\text{对照侧根数量}} \times 100\%$$

5.2.4 优选化合物对种子根中内源激素含量的影响

材料的培养与处理

每个培养皿中加10 mL药剂溶液，空白用蒸馏水为对照，黑暗条件下培养，培养温度为 22 ± 2 °C。从药剂处理时开始计算，取样时间分别为：0 h、24 h、48 h、72 h和96 h，取样前准备好液氮及装样锡箔纸并做好标记，取样时将取好的样速冻到液氮中，趁低温将样品包装好并存储于-80°C备用。

植物内源激素(IAA、GA₃、ABA和ZR)测定

样品前处理准确称取1.0g（精确至0.01g）样品剪碎，液氮冷却条件下研磨，然后加入10mL甲酸-乙腈匀浆3min，4°C浸提过夜。加入4.0g MgSO₄、1.0g NaCl，涡旋混合1min。5000r/min下离心5min后，过C18小柱，过滤待测。

测定方法

种子根中内源激素含量采用液相-质谱联用技术测量，LC-MS 型号为 Shim-ParkC18VP-ODS, 色谱柱的规格为(150 mm×4.6 mm, 5μm)，检测器SHI-MAZUSPD-10A (λ=254 nm)。四种激素(IAA、GA₃、ABA和ZR)标准溶液的浓度分别为：10 μg/L、50 μg/L、100 μg/L、200 μg/L、500 μg/L 和 1000 μg/L。流动相为甲醇和0.0075%乙酸（体积



比为45:55)，流速为0.25 mL/min，柱温为30 °C，进样量为10 μL。以出峰时间定性，峰面积定量。

5.2.5 优选化合物初步毒理评估

毒理试验过程及判断标准参照《农药登记毒理学试验方法 GB 15670》进行。

5.2.6 优选化合物对种子萌发的调控

根据初次活性筛选结果，选取在适宜浓度下对种子根长促进作用最大的有机硒功能试剂，根据文献分别统计1d、2d、3d、4d、5d、6d和7d的种子发芽的数量，计算种子的发芽势、发芽率、发芽指数以及活力指数。

$$\text{发芽势(Gv)} = (\text{第4d发芽种子数} / \text{供试种子数}) \times 100$$

$$\text{发芽率(Gr)} = (\text{第7d发芽种子数} / \text{供试种子数}) \times 100$$

$$\text{发芽指数(Gi)} = \Sigma(\text{Gt}/\text{Dt})$$

其中，Gt为第t日的发芽种子个数，Dt 为相应的发芽日数；

$$\text{活力指数(Vi)} = \text{发芽指数(Gi)} \times (\text{第7 d胚根的长度})。$$

5.2.7 优选化合物对植株表型测定

(1) 株高、生物量和根冠比采用直尺法，总根长度测量采用扫描仪(型号为EPSON1680)及其配套的 WinRhizoPro5.0 根系分析软件扫描计算获取。

(2) 叶片叶绿素荧光、光合作用各指标均采用 Li-6400(LI-COR, Lincoln, USA)便携式光合作用仪测定。叶绿素荧光各指标包括初始荧光(F_0)、最大荧光(F_m)、PSII原初光能转化效率(F_v/F_m)、潜在光化学转化效率(F_v/F_0)、光化学猝灭系数(qP)和非光化学猝灭系数(qN)；光合作用参数包括：净光合速率(P_n , $\mu\text{mol}/(\text{m}^2 \cdot \text{s})$)、气孔导度(G_s , $\text{mol}/(\text{m}^2 \cdot \text{s})$)、气孔阻力(R_s , $(\text{m}^2 \cdot \text{s})/\text{mol}$)、蒸腾速率(T_r , $\text{mmol}/(\text{m}^2 \cdot \text{s})$)、胞间二氧化碳浓度(C_i , $\mu\text{mol}/\text{mol}$)。测定时间为上午9:00-11:00。选取各处理植株的全展三重复叶进行测定，每个处理3次重复。

5.3 中度盐胁迫条件下有机硒功能试剂对水稻缓解效应探究

试验采取单因素随机取组设计，选择完整、大小一致的水稻种子，并用 2%的次氯酸钠水溶液消毒 10min，再用双重蒸馏水漂洗 30min(10min×3 次)。试验共设计 6 个处理，分别是 S1(0μM G-6+H₂O)；S2(0ppm G-6+150mMNaCl)；S3(0.5ppmG-6+150mMNaCl)；S4

(1.0ppm G-6+150mMNaCl), S5(2.0ppm G-6+150mMNaCl); S6(5.0ppm G-6+150mM NaCl)根据前期的预试验, 我们选择中度盐胁迫(150mMNaCl)浓度作为试验胁迫条件。

5.3.1 生理生化指标

盐胁迫处理 48h 后开始取样用于生理生化指标的测定。取水稻根和叶片作为试材, 每个处理样品取足 1.0g (以鲜重计算), 迅速冷冻于液氮中, 包装、标记后转移至低温存储设备保存备用。

生理生化指标包括: 过氧化氢(H_2O_2)、超氧阴离子($O_2^{\cdot-}$)、丙二醛(MAD)、抗坏血酸(ASA)、脱氢抗坏血酸(DHA)、还原型谷胱甘肽(GSH)、氧化型抗坏血酸(GGSG)的含量; 超氧化物歧化酶(SOD), 抗坏血酸过氧化物酶(APX), 过氧化物酶(POD), 谷胱甘肽巯基转移酶(GST), 过氧化氢酶(CAT), 谷胱甘肽还原酶(GR)的活性。

5.3.2 水稻体内 GSTs 相关抗氧化应答基因的筛选

根据 NCBI 注释以及文献报道查找模式植物拟南芥中与逆境胁迫应答相关的 GSTs, 然后将 NCBI 收录水稻 GSTs 蛋白序列与拟南芥逆境胁迫应答 GSTs 蛋白进行聚类对比分析。分别依次利用 MEGA X32 软件聚类分析, BioEdit 软件序列对比评分筛选出水稻可能的抗胁迫应答候选谷胱甘肽巯基转移酶蛋白序列, 并将其对应的基因用于实时荧光定量 q-PCR 的检测。

5.2 拟解决的问题

本课题组前期已经成功研发了水溶性有机硒功能试剂, 验证了有机硒试剂可以提高植物抗病能力和营养价值。要解决的关键问题是技术成果如何有效地应用于水稻种子和苗期的生长, 由于水稻的生长环境比较复杂, 要有效发挥有机硒的功能, 需要确保有机硒优良的稳定性、生态安全性, 以及叶面内吸输导性。

(1) 有机硒的稳定性和生态安全性问题

有机硒中硒的价态是负二价, 对环境中氧、水汽、热、光等敏感, 通常不稳定, 容易被氧化脱硒。有机硒被氧化脱硒后会失去抗病功能和对水稻生长强化的功能。本项目将发展有机硒与水稻必须的矿物质元素耦合的稳定化技术, 以及有机硒微乳化的稳定技术, 开发出稳定的有机硒功能试剂, 解决有机硒的稳定性问题, 使其在复杂的生长环境下有效发挥作用。

(2) 有机硒的水溶性和内吸输导性问题

要使有机硒能被水稻有效利用，必须开发水溶性的有机硒试剂并提高其在叶面的黏附力和内吸输导性能。目前，项目团队已经开发出水溶性优异且稳定的有机硒试剂，在此基础上优化试剂配方可以有效提高叶面的内吸疏导性能。

5.3预期成果

- (1) 研发出调控水稻抗逆生长的有机硒功能试剂；
- (2) 发表高质量研究论文1篇。

6 进度安排：

2024年5月-2024年10月

在原有工作基础上，设计和开发可抗逆的仿植物激素有机硒功能试剂，测试其生物活性及其对农作物的调控作用，进而优化试剂配方，在此阶段解决大部分关于试剂高剂量安全性、稳定性、水溶性等方面的问题。

2024年10月-2025年3月

将功能试剂拓展应用于水稻，完成试剂对水稻抗盐碱效果的研究。对比普通水稻种子和苗期的生长状况，找出试剂的优点和劣势，通过优化试剂结构解决给植物带来的劣势，最终做到试剂的使用是益于水稻的。并测试该试剂是否与水稻内源激素相互兼容，在此试验基础上继续优化试剂配方，解决生物兼容性的问题。

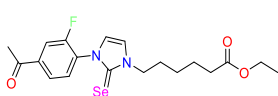
2025年3月-2025年8月

继续完成抗逆效果研究并探究试剂浓度对水稻的生长调控，寻找作用水稻的最适试剂浓度。在此阶段研究后，预期可提升水稻种子和苗期生长时的抗逆效果，在此阶段总结发现并解决问题，完善研究内容，最终完美结题。

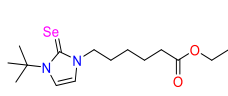
7 已有基础：

7.1 本项目的研究积累

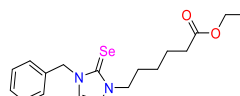
7.1.1 部分已合成的有机硒功能试剂结构表征(NMR)



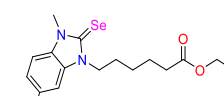
G-4.



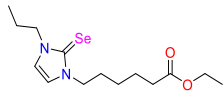
G-5.



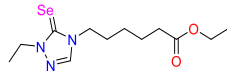
G-6.



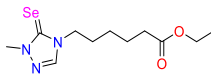
G-7.



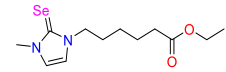
G-8.



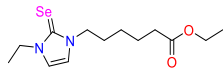
G-9.



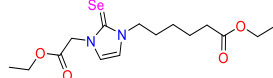
G-10.



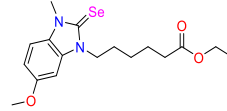
G-11.



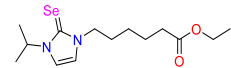
G-12.



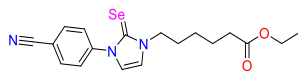
G-13.



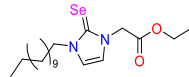
G-14.



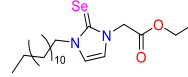
G-15



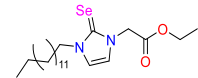
G-16.



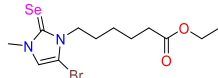
G-17.



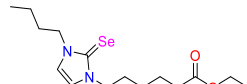
G-18.



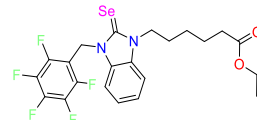
G-19.



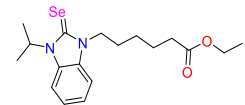
G-24.



G-25.



G-26.



G-27.

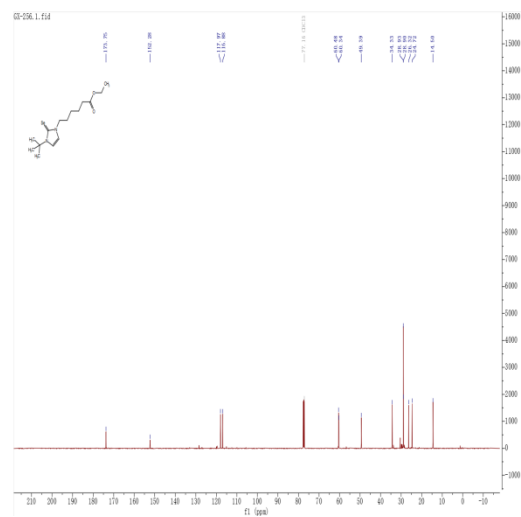
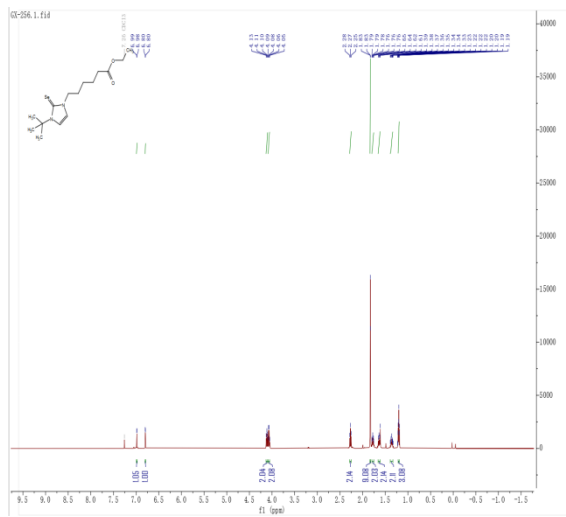


图 5

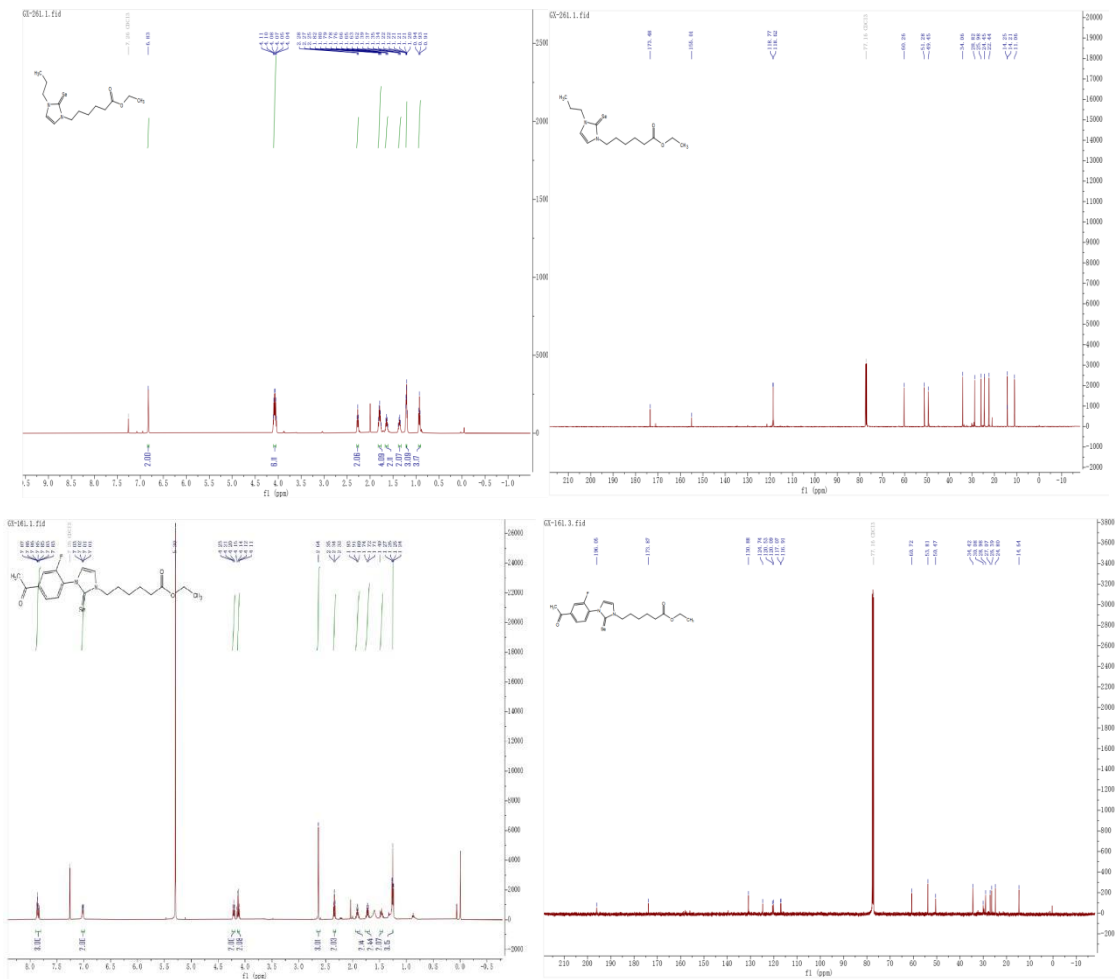


图 5

7.1.2 蛋白质-小分子对接

在蛋白质-小分子对接中表现（图6），G-6分子与GSH-Px强结合能为7.2KJ/mol，通过分子模拟的手段可以推测，有机硒功能试剂与靶标蛋白的结合能非常高，为进一步开展工作提供了理论依据，具有重大参考意义。

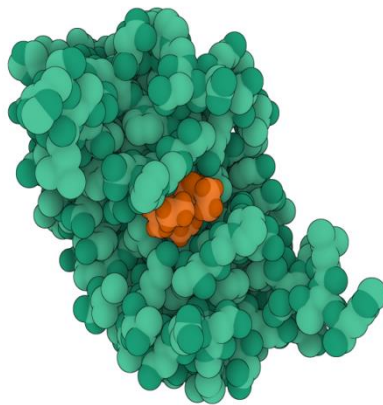


图 6 G-6分子与GSH-Px的分子对接

7.1.3 有机硒化合物的自由基离子清除实验(DPPH)

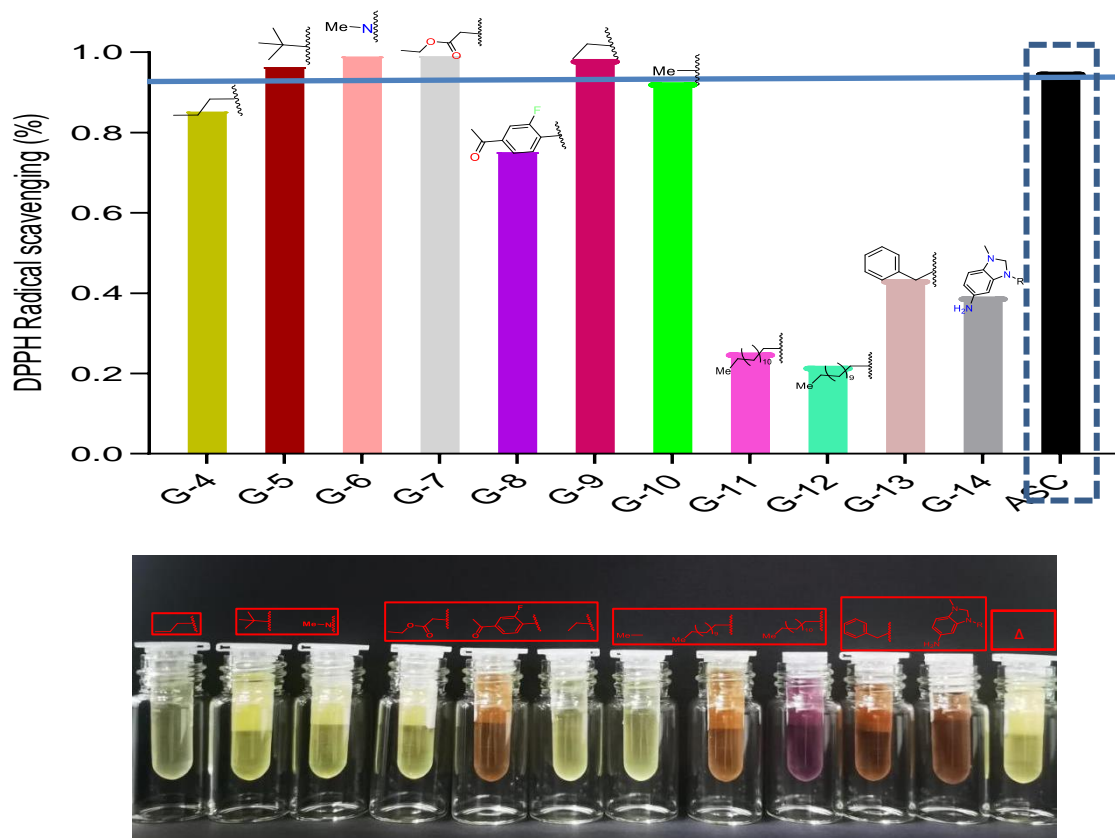


图 7 自由基清除实验



7.1.4 纸上催芽法实验，证实外源有机硒功能试剂提高水稻种子在盐胁迫下的发芽势（如图8，9，10）

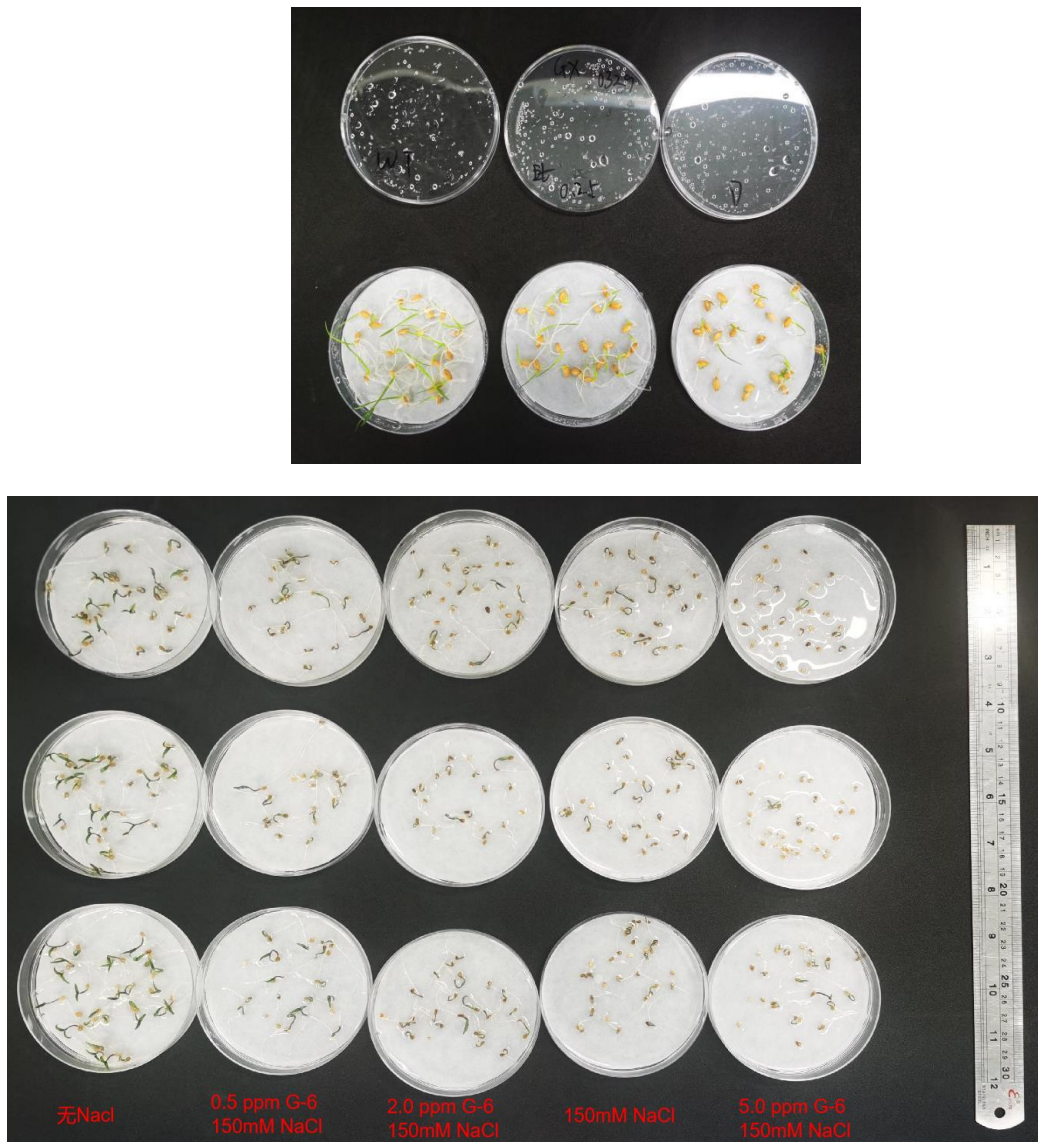


图 8 盐胁迫下，外源有机硒功能试剂对水稻发芽影响

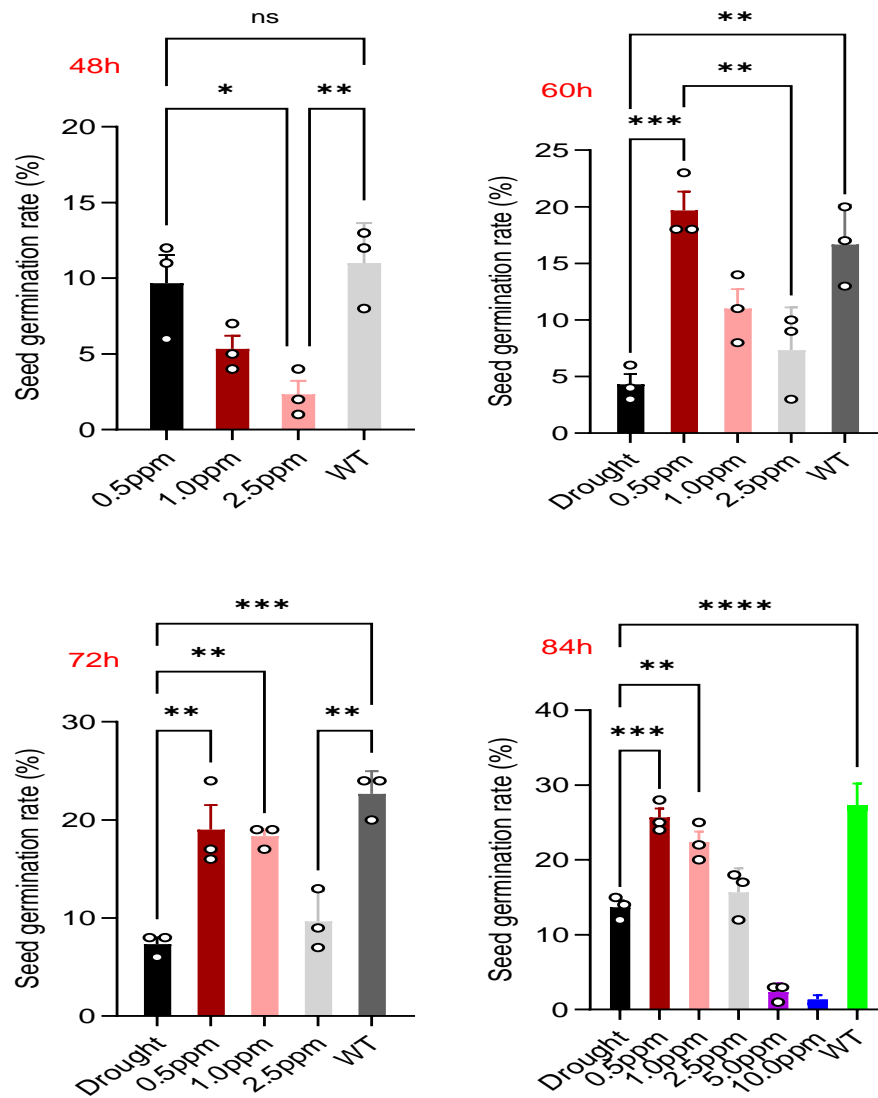


图 9 种子发芽率

如图 9 所示，施用0.5ppm的有机硒试剂，水稻种子发芽率最佳。



图 10 抗盐胁迫生长

(4) 本实验室研究团队前期已经成功研发了水溶性有机硒功能试剂，验证了有机硒试剂可以提高植物抗病能力和营养价值。

(5) 有机硒功能试剂在农业领域的应用研究成果

项目团队所在课题组在有机硒活性化合物及其应用方面有扎实的研究基础，已经申请发明专利9件，目前获得授权发明专利8件，发表SCI论文3篇。成果如下：

发明专利：

(1) 一种唑硒酮功能试剂及其应用，中国发明专利，申请号：202211434442.8

(2) 一种具有杀虫、杀菌和除草功能的N-二氟甲基三氮唑硒脲化合物及其用途，申请号：202110783471.4，授权日期：2022年12月13日

(3) 一种三氮唑硫（硒）酮衍生物的制备方法，中国发明专利，专利号：ZL202010424474.4，授权日期：2021年6月25日

(4) 一种咪唑硫（硒）酮衍生物的制备方法，中国发明专利，专利号：ZL202010424469.3，授权日期：2021年6月25日

(5) N-二氟甲基唑类硒脲衍生物或农药学上可接受的盐及其用途，中国发明专利，专利号：ZL202011222204.1，授权日期：2021年2月2日

(6) 一种N-二氟甲基咪唑硫（硒）脲衍生物的制备方法，中国发明专利，专利号：ZL202010944657.9，授权日期：2021年1月8日

(7) 一种N-二氟甲基唑类硫（硒）脲衍生物及其制备方法，中国发明专利，专利号：ZL201811452050.8，授权日期：2021年1月22日

(8) 苯并咪唑酮衍生物或农药学上可接受的盐及其用途，中国发明专利，专利号：ZL202010743473.6，授权日期：2020年11月24日

(9) 一种唑类硫（硒）酮衍生物及其制备方法和应用，中国发明专利，专利号：ZL201810648408.8，授权日期：2020年8月18日

学术论文：

(1) Guo Xue-Ying, Huang Zi-Hao, Xiong Lan-Tu, Dong Li, Huang Yue-Kun, Wei Lin-Hao, Tang Ri-Yuan*, Wang Zhi-Lin, Xu Han-Hong, Azole selenourea disrupted the midgut and caused malformed development of *Plutella Xylostella*, *J. Integr. Agric.*, 2023, 22, 1104.

(2) Zi-Hao Huang, Xue-Ying Guo, Lan-Tu Xiong, Li Dong, Jin-Tong Jian, Lin-Hao Wei, Ri-Yuan Tang* and Han-Hong Xu, Versatile Triazole Selenoureas against Pests, Fungi, and Weeds, *ACS Agric. Sci. Technol.*, 2022, 2, 754.

(3) Jin-Tong Jian, Lan-Tu Xiong, Xue-Ying Guo, Yi-Lin Ma, and Ri-Yuan Tang*, Triazole Selenourea as a Nutritional Fortifier and Defense for the Microgreen of Chinese Flowering Cabbage, *ACS Agric. Sci. Technol.* 2023, 3, 11, 1044–1054.

7.2 已具备的条件，尚缺少的条件及解决方法

本团队所在科研室具备项目开展的所有软硬件条件，能顺利完成各项研究任务。

三、 经费预算

开支科目	预算经费（元）	主要用途	阶段下达经费计划（元）	
			前半阶段	后半阶段
预算经费总额	10000.00		5000.00	5000.00
1. 业务费	5000.00		2500.00	2500.00
（1）计算、分析、测试费	2000		1000	1000
（2）能源动力费	0			
（3）会议、差旅费	0			
（4）文献检索费	0			
（5）论文出版费	3000		1500	1500
2. 仪器设备购置费	0			
3. 实验装置试制费	0			
4. 材料费	5000		2500	2500
学校拨款				
财政拨款				



华南农业大学
South China Agricultural University

四、项目组成员签名

钟锦豪 张欣欣 杜宇默 胡汶琪 杨蕾

五、指导教师意见

同意申报。

导师 (签章):
2024 年 5 月 5 日

杨波

六、院系推荐意见

盖
年 月 日

七、学校推荐意见

盖
年 月 日

附件 1

广东青年大学生“百千万工程”突击队行动

突击队选派登记表

所在学校	华南农业大学	所属院系	材料与能源学院		
需求单位	蓝坊镇人民政府	服务地址	程坑三华李基地		
团队名称	华南农业大学新“晒”望实践队				
主要服务领域 (可多选)	<input checked="" type="checkbox"/> 岭南特色产业 <input type="checkbox"/> 海洋产业 <input type="checkbox"/> 乡村集体经济 <input type="checkbox"/> 绿美广东 <input type="checkbox"/> 县域科技服务 <input type="checkbox"/> 乡村规划建设 <input type="checkbox"/> 文化创意和保育 <input type="checkbox"/> 古建筑活化 <input type="checkbox"/> 乡村公共服务 <input type="checkbox"/> 决策咨询				
特色项目 (可多选)	<input type="checkbox"/> “挑战杯”落地项目 <input type="checkbox"/> “互联网+”落地项目 <input checked="" type="checkbox"/> “攀登计划”立项项目				
团队成员	队长				
	姓名	性别	院系	联系电话	身份证号
	马意林	女	材料与能源学院	18819525300	513723199811010023
	队员				
	姓名	性别	院系	联系电话	身份证号
	邓青青	女	材料与能源学院	18565471805	441823199805270027
	郑雪芬	女	材料与能源学院	19878838932	440513200102051544
	钟媛菲	女	材料与能源学院	18007601965	441427200102010041
	聂彬恒	男	材料与能源学院	18938432072	441226199906010319



	闫浩然	男	材料与能源学院	18372272031	420624200011255112
	刘振	男	材料与能源学院	13722954447	130622199904050213
	张欣欣	女	材料与能源学院	13437870420	440882200205300047
	黄永杰	男	材料与能源学院	13729714207	445302200309250019
	胡汶琪	女	材料与能源学院	13042045773	44188120040506002X
指导老师	姓名	职称	院系	联系电话	备注
	汤日元	教授	材料与能源学院	13825112030	带队老师
	杨波	副教授	材料与能源学院	18818914392	
实践项目介绍		<p>(包括但不限于项目名称、服务方案、集中实践计划等, 1000 字以内, 详细方案可另附页)</p> <p>我国土地总体缺硒或者贫硒, 含硒的土地通常是点状分布, 很难标准化生产高品质农产品; 亚硒酸盐高毒, 有生态安全风险。为了解决这一问题, 本团队开发了系列绿色、安全的有机硒试剂, 研究发现该试剂可以有效调控农作物的生物合成, 显著改善农产品的功能活性成分结构, 极大提高农产品精深加工价值。</p> <p>测试有机硒功能试剂的生物活性及其对农作物的调控作用, 到合作建立的成果转化基地梅州蕉岭县程坑农业专业合作社开展田间规模化试验, 探究功能试剂对三华李不同生长阶段的影响, 并对果品质量进行评价, 从而优化试剂配方。将优化的有机硒功能试剂在梅州地区对多品类农产品种植进行规模化应用示范。将富含有机硒功能成分的农产品深加工成高附加值的产品。</p>			



	<p>团队通过与梅州农林科学院蔬菜研究所合作将功能试剂在梅州地区进行应用，以菜心、番茄、三华李、柚果等农作物为研究对象，探究果蔬吸收同化有机硒后的抗病能力、生长调节、营养强化、以及功能硒形态，结合水培、滴灌、叶面喷施等种植技术手段，调控果蔬中的生物转化，强化功能有机硒、多酚、黄酮、可溶性糖等活性成分，最终生产出高品质农产品。并对研究成果进行推广应用，通过成果转化基地的示范引领作用，带动周边农户科技兴农，从而实现农业的高质量发展。同时，与广州汇标检测技术中心研究院合作，分析检测农作物的功能成分，为高品质农产品的标准化种植提供数据支撑。</p>
指导老师 意见	<p>同意</p> <p>签章：[Signature]</p> <p>2024年5月23日</p>
院系意见	<p>同意</p> <p>盖章：[Red Stamp: 农业大学]</p> <p>2024年5月23日</p>
学校团委 意见	<p>(学校团委须收到需求单位的“结对确认函”后方可审核通过)</p> <p>盖章：</p> <p>年 月 日</p>



附件 2

广东青年大学生“百千万工程”突击队行动 结对确认函

共青团华南农业大学委员会：

我委已收到贵校新“晒”望实践团队投递的项目方案，经对接洽谈，该实践团队的项目方案符合共青团蕉岭县蓝坊镇委员会提出的提高三华李品质，推动产业发展需求，双方已达成结对意向，现予以回函确认。

请贵校提醒团队在约定时间内到达实践地点报到。

需求单位联系人：

李婕妤

联系方式：

18138695969

服务地点：

梅州市蕉岭县蓝坊镇

特此函达，感谢贵校对基层高质量发展的大力支持。

共青团蕉岭县蓝坊镇委员会

2024年5月23日





09:36

华农大农技通

姓名	所在单位	角色
廖鑫	材料与能源学院	参与人
戴金玲	材料与能源学院	参与人
杨波	材料与能源学院	参与人

服务总结

开展培训/讲座次数：1

培训人数：100

服务总结：材料与能源学院招生队伍到珠海科技学院开展招生宣传

审核历史信息

审核部门	审核时间	审核意见
材料与能源学院	2024-11-27	审核通过
华南农业大学	2024-11-27	审核通过